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Original Communications

PHLEGMASIA ALBA DOLENS AND THE RELATION OF THE LYMPHATICS TO THROMBOPHLEBITIS*

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THROMBOPHLEBITIS may be defined as an association of thrombosis with an inflammatory change in a vein's wall. As to which is usually the primary process, that is, whether the thrombosis or the inflammation is at the bottom of the trouble, has never been settled. Although some states of the blood undoubtedly predispose to thrombosis—a matter as to which Bancroft[1] has recently made a very full report—some local factor in or about the vessel's wall would seem to be the immediate exciting cause. Every one has necessarily been rather vague in speaking of this factor, which is more often, perhaps, infectious than traumatic or degenerative. What used to be called marantic thrombi, for instance, thrombi which form in the veins of patients depressed by systemic disease, have been shown so many times to be associated with the presence of bacteria in the vessel's wall as to bring the element of infection very much to the fore. And, of course, the familiar milk-leg is even more often suspected of being secondary to uterine sepsis. But it is far from true that all sorts of thrombophlebitis have a bacterial origin. Indeed, among the several forms of the disease presently to be described are more than one with which infection appears to have little to do.

In all, there may perhaps be five principal varieties of thrombophlebitis:

(1) Thrombophlebitis in varicose veins;

(2) Phlebitis migrans;

(3) Thrombosis due to injury;

(4) Thrombophlebitis in previously normal superficial veins;

(5) Phlegmasia alba dolens, for which the synonyms are milk-leg and deep (iliac or femoral) thrombophlebitis.

Of all these varieties the last is decidedly the most interesting as well as the most serious and disabling. The others will therefore be discussed first.

*From the Surgical Service of the Peter Bent Brigham Hospital, Boston. Read before the New York Academy of Medicine, October 23, 1931.

THROMBOPHLEBITIS IN VARICOSE VEINS

Very commonly indeed, thrombosis occurs in the varicose saphenous vein or some of its branches. The process is liable to begin in a very superficial tortuous vessel of the calf or lower thigh and to advance upward. Exceptionally, thrombosis does not reach the groin, but since it is always likely to progress until it meets a vigorous current, it will usually be found, if given time, to have involved the saphenous vein up to its entrance into the femoral, which, however, it never seems to enter. From a thrombosed varicose vein embolism is rare.

The cause of thrombosis in varix is undoubtedly the unhealthy state of the vessel's wall. As this becomes scarred and stretched, the endothelial lining may readily be cracked or even destroyed at some one spot, permitting blood to clot, and from this point thrombosis spreads. In a process of this sort infection is quite as likely to be secondary as primary except, perhaps, in the presence of a septic ulcer. On the whole, the evidence is that it is usually mild and unimportant. Sometimes, of course, the skin becomes red and hot over the thrombosed vessel, and the clot softens, breaking down in the end and calling for drainage. Most often the skin becomes somewhat adherent, showing a little pinkish color which soon fades to a pale brown. A moderate induration surrounds the vessel, which can be felt as a solid, tortuous cord.

In contrast with some other forms of thrombophlebitis, this sort never causes edema of the leg, and though it is anticipating the subsequent story to offer an explanation, it would seem that the superficial lymphatics, which accompany the principal venous channels, are not disturbed by inflammatory processes within varicose veins. It must be that in the course of the dilatation and sclerosis which the varicose vein undergoes, the lymphatics about it are gradually destroyed, their function being taken over by other channels. Otherwise considerable swelling of the lower leg would be inevitable.

As every one knows, the course of phlebitis in varicose veins is prolonged, tedious, subject to recurrence, and requires, or seems to require, rest in bed. Nor are the veins permanently obliterated for the future. Being readily canalized, they soon resume their former appearance and character. It is therefore advisable, on meeting this sort of phlebitis in its early, acute state, to put the patient to bed, to use heat to relieve discomfort and to quiet the local inflammation, and when in the course of perhaps a week, the vein can be felt as a firm cord, to remove it by a formal operation. There is every reason not to use the traditional ice-bag. It devitalizes the tissues, interferes with nature's process of repair, probably causes thrombosis to spread and gives less comfort than does heat.

To obviate embolism, the operation should begin at the saphenous opening, and if the skin at any point is adherent to the thrombosed vessel, it should be excised with the vein, making a clean wound. Such op-

erations greatly shorten the patient's disability and cure the varicosity besides. They can be performed, if necessary, under local anesthesia.

There are, however, satisfactory and less radical means of treatment. Fischer[4] has recommended making local pressure at what seems to be the upper limit of the thrombosis by infolding the skin with adhesive plaster, just as is done for umbilical hernia in an infant, enclosing the leg below this level in adhesive strapping and letting the patient go about as usual. Jaeger[9] substitutes an "elastoplast" bandage for the enclosing adhesive plaster. He reports favorable results in more than 100 cases, finding that embolism does not occur. Another variation upon this scheme has been suggested by O'Neil.[14] He injects a sclerosing chemical into the vein above the thrombosed part—all these methods seem to depend on identifying this level, a matter not always easy—in order to destroy locally the varicose vessel and limit extension of the thrombosis; then he applies a "Klebro" bandage as under the German system. He too reports excellent immediate results.

PHLEBITIS MIGRANS

This curious disease is most often seen as a complication of thromboangiitis obliterans. Upon any part of the limbs there may appear a tender, sore thickening in the course of a vein. There may even be a rough symmetry between two opposing extremities. The vein seems to be occluded, although in the one specimen I have excised no thrombus was found. For several days or even weeks the process remains stationary or progresses a little, without much regard to treatment. Then it is likely to jump to a new spot higher up and to disappear below. Those who have suffered from many attacks are inclined to pay no more attention to the disease than they are obliged to. Short of massage, which has been known to excite embolism, such use of the part as the inevitable soreness allows, seems justifiable. No local treatment is of much help, though rest and warmth are grateful. Even in individuals whose Buerger's disease seems to have become, in most respects, stationary, phlebitis migrans may recur indefinitely.

But not all thrombophlebitis of this sort is related to thromboangiitis obliterans. Equally curious local migrating and recurring forms appear, usually in males, coming on in early adult life and returning at irregular intervals thereafter. These persons have blood, or veins, of such a character that thrombosis readily occurs, particularly in the superficial vessels of the legs. As a rule, only a short length of vein is involved and there is little reaction about it. Trauma often excites the inflammatory process and therapeutic intravenous injections of almost any sort are liable to induce it. In the few patients of this kind whom I have seen, pulmonary infarctions have been rather common. No effective treatment is known, though vaccines made from bacteria of the patient's tonsils or root abscesses have been used with reported success.

THROMBOSIS DUE TO INJURY

Odd sorts of injury rarely lead to thrombosis of even the deep veins. My own experience has been entirely with thrombosis within the muscular aponeurosis of the lower leg: on two occasions, after fracture of a metatarsal bone, and on another, after vigorous massage. A fatal embolism resulted in one instance and the postmortem examination showed that most of the numerous veins among the muscles were thrombosed.

If the patient undertakes to go about in such a state, that part of the leg below the knee becomes somewhat cyanotic, full and slightly edematous. Discomfort is usually marked. On going to bed, these signs almost completely disappear, leaving only the slightest cyanosis and some degree of deep tenderness. This appearance of quiescence is deceptive, however, for if the patient tries again to get about, the original signs reappear. Recovery may be slow; so slow, indeed, and so subject to recurrence that, after one patient had died of embolism, the femoral vein of another was ligated in Hunter's canal. Recovery seemed to be hastened by this step, but its principal advantage is that it offers insurance against pulmonary infarction or embolism.

These three sorts of thrombosis, or thrombophlebitis, much as they differ from each other, differ still more from the varieties now to be described, in which edema is a feature and involvement of the lymphatics appears to be a fundamental part of the disease.

THROMBOPHLEBITIS IN HITHERTO NORMAL SUPERFICIAL VEINS

Thrombophlebitis in hitherto normal superficial veins is placed in a category by itself, partly because, though rare, it is a serious disease and partly because its description will aid in making clear the distinction between superficial phlebitis and phlegmasia alba dolens, a matter, as to which, in the past, there has been a great deal of confusion.

The serious quality of an extensive superficial phlebitis in veins hitherto quite normal lies in the lymph-stasis and ulceration which usually follow the acute attack. As will appear later, the veins and large lymph-trunks are closely associated, so that anything affecting the one necessarily involves the other. And whether or not thrombosis occurs in the superficial veins because of a lymphangitis about them or whether the lymphatics are secondarily involved in a violent inflammatory reaction of the vein's wall, the fact remains that local and general lymph-stasis of the superficial tissues drained by the great saphenous vein is likely to follow an active thrombophlebitis in that vein. During the attack, the skin over the course of the main vein and its principal branches is liable to be red, hot and indurated. After the attack has subsided, as the patient begins to get about, edema, induration and pigmentation in the particular areas drained by the lymphatics associated with the saphenous

system set in, and ulceration sooner or later follows. Ulcers and residual induration should be treated after the methods which have been found so useful[6, 7, 8] in the management of postphlebitic induration and ulceration in general and to which presently reference will be briefly made.

The background of a superficial thrombophlebitis is, as a rule, a debilitating disease, injury or operation, whether or not associated with sepsis, but it is uncommon enough to have been very little studied. Probably the superficial and the deep disease have often been confused. Actually they should never be, for, in a superficial thrombophlebitis, the reaction about the superficial veins, that is, the great saphenous system,

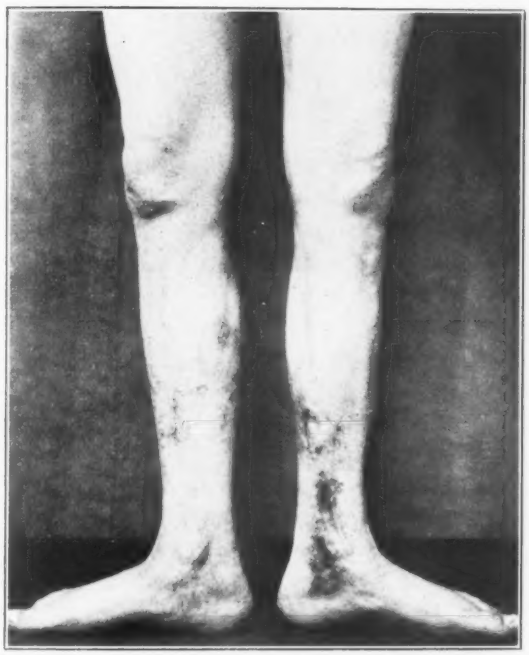

Fig. 1.—Generalized thrombophlebitis of the superficial (nonvaricose) veins—the late result. Pigmentation and scar formation mark the course of the lymphatics accompanying the superficial veins. This is especially evident in the left leg.

is perfectly evident, as well to the eye as to the touch. The veins, in at least some part of their course, are palpable as hard, tender cords; and some visible redness or pigmentation of the skin is always present. What cause confusion are the tenderness and pain so often evident during a deep phlebitis over the femoral vessels in Hunter's canal. Unfortunately the femoral canal is directly beneath the usual course of the great saphenous vein, so that when the physician palpates the inner face of the thigh, finding acute tenderness extending from the groin nearly down to the knee, he believes the process to be superficial, whereas, unless the saphenous vein is actually palpable, it is invariably deep.

PHLEGMASIA ALBA DOLENS*

The nature of this ancient disease, with its sonorous title, has long excited the interest of the medical profession but seems latterly to have been given up as a bad job. Under the guise of milk-leg, its cause once seemed plain enough. Cruveilhier[3] described it as an iliac thrombosis, an accidental extension from a beneficent postpartum clotting in the great uterine venous sinuses. And when Pasteur[15] had laid uterine sepsis to the streptococcus, and Widal[17] and others had discovered these bacteria in the walls of thrombosed uterine veins, the bacterial origin of a thrombophlebitis of the great pelvic veins could quite reasonably be explained. For it seemed plain that thrombophlebitis of the uterine veins must then have progressed into the common iliac, obstructing the venous return from the leg. But phlegmasia alba dolens is by no means confined to the puerperium, nor is it even confined to females. It is liable to occur in individuals of young adult life and middle age, who are for any reason long confined to bed, particularly by debilitating diseases, whether or not infectious, by operations and by injuries. And in these persons it differs in no way from its puerperal form.

It has a rather characteristic course which varies in severity from case to case. As a rule, although the clinical signs are often missed, the disease begins with an elevation of pulse and temperature which may last twenty-four or forty-eight hours. Then pain sets in, usually referred to the thigh, the groin, the knee, the calf, sometimes the perineum. This may creep on, associated with a dead, heavy feeling in the leg or it may be so severe as to resemble a sudden arterial ischemia, leaving the leg totally powerless. In twenty-four to forty-eight hours more, swelling begins, and in another day or so, the whole picture of phlegmasia alba dolens is established.

Swelling affects the entire leg, thigh, calf and foot. In its severest form, tension is so great that there is no pitting on pressure. The leg can hardly be moved, not only on account of the discomfort but because of its great size. With disease of a milder sort, tension is much less, and after a few days of mild pain, discomfort on attempted motion and moderate swelling, improvement sets in. By the end of two weeks, this mild disease, except for a little residual swelling on getting about, is over. But with the severer forms the outcome is quite different. For weeks, even months, the huge white limb remains unchanged, subsiding only to leave behind so much edema that the leg, though useful enough, must be spared and nursed thereafter.

What first attracted my attention to phlegmasia alba dolens were its late complications, that is, the states of local edema, induration and ulceration which occur six months, a year, two years, even ten years later.

*In the following discussion, the painful white inflammation of a limb is described as if it occurred only in the leg. A somewhat similar but far milder disease I have twice noticed in the arm. It has hardly been described or studied, except in the serious permanent form which it assumes as a sequel to operations for cancer of the breast.

With these, no venous stasis or obstruction is associated; rather do they have the appearance of local lymph-stasis. Such a lesion is liable to appear first as a porky area upon the inner face of the calf over which the skin repeatedly desquamates. This area enlarges and other patches may form. Soon pigmentation occurs and finally ulceration which may be very extensive, painful and intractable. This progressive change apparently is due to local nonsuppurative infection superposed upon a chronic generalized lymph-stasis, which may have been very obvious or

Fig. 2

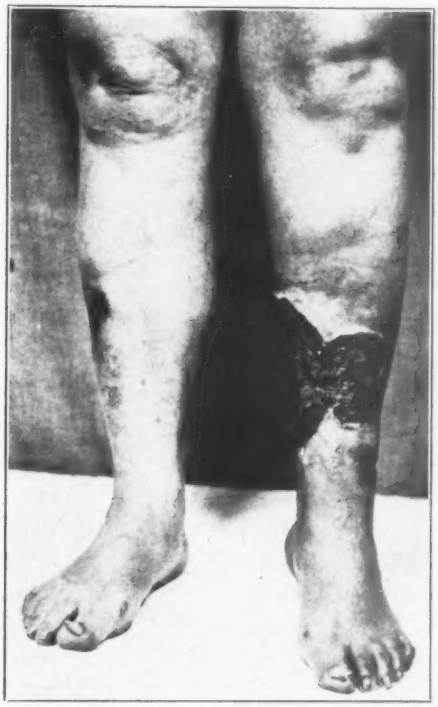

Fig. 3

Fig. 2.—Postphlebitic edema after phlegmasia alba dolens in a typical situation—at an early stage. At the moment, the edema is receding, and desquamation of the skin is going on.

Fig. 3.—Postphlebitic edema and induration after phlegmasia alba dolens—a very advanced stage of ulceration. Such ulcers are best treated by a wide excision including the deep fascia, followed by a skin graft.

hardly noticeable. It seems to correspond, in a local form, to elephantiasis, which, it is generally agreed, results from repeated attacks of cutaneous infection in a limb already engorged with lymph. Obstinate ulcerations call for wide excision down to the unchanged tissues just beneath the deep fascia and for skin grafting or plastic operations. Local states of superficial edema and induration without ulceration can be treated with success, provided the deep lymphatics are open, by Kondoleon's[10] excision of deep fascial strips. Such treatment has been described in earlier publications.

Matas[13] was the first to recognize that lymph-stasis might follow upon thrombophlebitis, taking forms of actual elephantiasis hitherto unrecognized because there was nothing tropical in their origin. Then Halsted[5] and his associate, Reichert,[16] in studying the edemas of the arm following operations for cancer of the breast, ingeniously brought out the fact that occlusion of veins has little or nothing to do with edema of a limb and that occlusion of the lymphatics has everything to do with it. For if a dog's leg were entirely divided at the level of the upper thigh, leaving only the bone and the bare femoral artery and vein, and promptly reunited with the meticulous care which Halsted held before the world as the ideal surgical technic, an edema like that of milk-leg would set in. This edema would disappear within ten days, owing to the connections which the lymph vessels were able promptly to establish across the scar, but the really astonishing finding was this: that if, at the moment when the swelling had nearly gone, the veins were divided, the edema, after a slight delay, continued to subside as usual. In other words, swelling came on while the veins were patent and disappeared while they were occluded.

With such evidence in hand, the nature of phlegmasia alba dolens takes on a new meaning. One need not deny that venous obstruction is present. It may be serious enough to cause an extensive and unsightly collateral circulation to appear upon the thigh, groin and abdominal wall. But usually, and as compared with the edema, it is insignificant. The *white* swelling of a deep thrombophlebitis is, in fact clearly of a lymphatic nature. Obviously the great lymph vessels draining the leg are obstructed. Now it is known that no lymphatics empty into veins in the extremities or indeed elsewhere than where the thoracic duct enters the junction of the left jugular vein with the subclavian. Therefore clotting in a vein of a limb cannot directly obstruct any lymphatics. The question then arises: Can venous obstruction of itself cause edema? Halsted's experiment suggests that it does not. Moreover, one may repeatedly make multiple ligations of an animal's common iliac, external iliac and femoral veins without causing any edema whatever, and on the only occasion upon which I have ligated the common femoral vein, in a human being, the leg became for the time very dark, but neither then nor later, did any edema appear.

It is true, on the other hand, that if a sufficiently severe inflammatory reaction is set up in the main vein of a limb, edema will certainly follow. This has been proved experimentally in animals (Leriche and Jung[12]; Reichert[16]; Homans and Zollinger[8]), so that up to the point to which the story has been carried, it might be held: (1) that the edema of phlegmasia alba dolens is due to involvement of the lymphatics in a violent inflammatory reaction originating in the thrombosed vein; or (2) that inflammation of the lymphatics is sufficient of itself to account for the great white leg and that thrombosis within the vein is altogether sec-

ondary to the reaction outside it. Such statements imply that there is a close association of the blood vessels and lymphatics, a matter which should now be discussed.

Embryologically, the lymph vessels draining the limbs bud from veins, and the main lymph-trunks are intimately related to both veins and arteries. To put the matter briefly, there is a superficial cutaneous network and there are delicate longitudinal vessels in the deep skin, a combination which the various forms of superficial lymphangitis have made familiar to every one; there is a deeper network lying upon the muscular aponeurosis which is perhaps responsible for the postphlebitic indurations to which allusion has already been made; there are larger lymph vessels, which accompany the superficial veins, running with the lesser saphenous vein into the popliteal space and with the great saphenous vein into the group of lymph nodes at the saphenous opening; and, finally, there are large, trunk-line lymphatics which pass up with the femoral vessels to the groin. Here all the lymphatics of the leg, both superficial and deep, must join, and having joined, they pass along the external and common iliac vessels through the iliac glands and on into the receptaculum chyli. Therefore, to bring about lymph-stasis of the entire leg, it is only necessary to block the larger lymphatics at some point between the saphenous opening and the aorta. This, of course, makes the relation between the great lymphatics and blood vessels of the pelvic brim particularly interesting.

To William Cruickshank[2]—William Hunter's pupil—we owe most of our knowledge of these relations. He followed the absorbents, as he called them, by injections of air and of mercury, and gives the following succinct description: "The large absorbents of the lower extremity are formed into two sets, superficial and deep-seated; the superficial set accompany chiefly the cutaneous veins, and the deep-seated accompany the arteries." As for the deep lymphatics, he says: "From the glands in the ham, two grand trunks . . . . run on either side of the femoral artery. These frequently communicate with one another by cross canals and their branches sometimes form circles which completely surround the artery." At the groin, the vessels he describes enter lymph nodes, emerging as two, four or even six trunks. From these there develops what he calls the "plexus iliacus externus."

Now if every one were not obsessed by the thought that phlegmasia alba dolens is a disease of the veins, the question might be raised whether it is not primarily a disease of the lymphatics. Suppose for a moment that there were such a thing as a deep lymphangitis—and no one seems to know whether there is or not—a violent inflammatory reaction would then take place actually within the arteriovenous sheath, affecting both the great vein and the artery of the limb. The vein, because of the active inflammation about it, would almost certainly become thrombosed, and the artery, if not thrombosed, might be thrown into a state of spasm.

At the same time, if the process took place at or above the saphenous opening, the whole leg would become swollen with lymph. Within the sheath, and depending upon the violence of the process, there would be an exudate, gluing together artery, vein and lymphatics. If this were

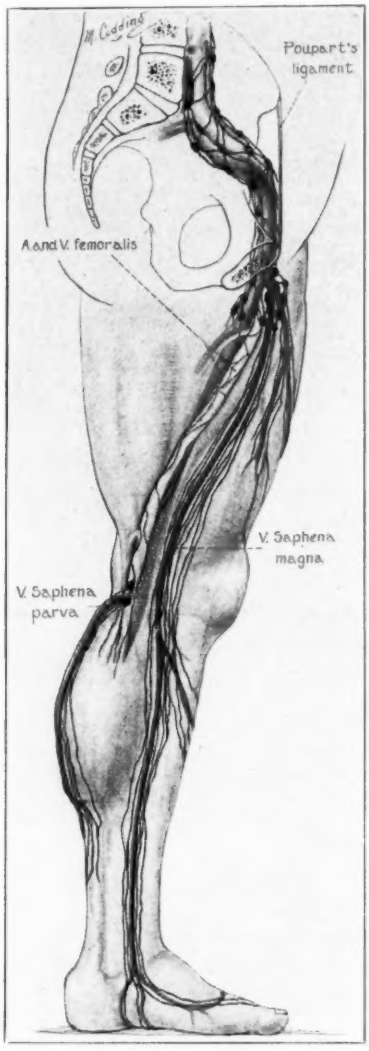

Fig. 4.—A semi-diagrammatic representation of the principal lymph vessels of the leg. The femoral artery and vein are indicated by a tone fainter than that of the superficial veins. The large femoral lymph vessels are shown as Cruickshank describes them, that is, closely surrounding the artery rather than the vein.

resolved, leaving little scar, no permanent disability would remain. If it became a densely organized scar, permanent lymph-stasis would follow.

Cruickshank[2] speaks of the lymphatics as being related to the great arteries rather than to the corresponding veins. Some years ago, a woman, about fifty years of age, presented herself at the Brigham

Hospital. Many years before she had suffered, in the course of a pelvic peritonitis, from phlegmasia alba dolens. The leg, however, had never been greatly swollen. The really striking change was toward ischemia. No actual pulsations could be felt at or below the left groin, and there was present, just above the ankle, an area of gangrene. In the course of a lumbar sympathetic neurectomy, which was of great benefit to her, it was possible to examine exactly the brim of the pelvis, where no sign of a vein could be made out and no suggestion of an arterial pulsation. Apparently both vein and artery had been destroyed by the earlier inflammatory process.

Obviously the most advantageous way to carry the matter further, was to examine, on the operating table, the state of the great artery and vein at the pelvic brim in a well-marked instance of phlegmasia alba dolens. Such an operation would be justified if it should prove that opening the arteriovenous sheath actually released local tension—a sort of *decompression*—and restored, in some degree, the flow of lymph.

By good fortune a young negro presented himself for treatment suffering from as high a grade of phlegmasia alba dolens as is often encountered. The disease complicated pneumonia, coming on with fever and with severe pain in the left leg, and leaving him, at the end of eight days, with a leg so tense that it neither pitted on pressure nor changed in any degree from day to day. The temperature remained steadily elevated between 100° and 101° F.

At the operation, the abdomen was opened a little to the left of the midline, exposing the left pelvic brim. As far as the left iliac vessels were concerned, all landmarks were obliterated. It was barely possible to feel the arterial pulsation, and whether or not a solid clot filled the vein was at first impossible to say. However, what seemed to be the sheath was finally split, revealing porky, lymph-soaked, vascular tissue so adherent to the great vessels that the vein was only discovered by accidentally cutting into it and the artery identified by its pulsation. The deeper coats of the vein seemed relatively normal, and a dark clean clot filled it solidly. In view of the vivid quality of the reaction about both artery and vein and the reactionless appearance of the clot, it seemed that the infection, if infection there were, must have begun outside the vein rather than within it; certainly the clot was the least striking part of the process. Opening the arteriovenous sheath proved quite difficult, owing to the very vascular exudate within and about it. The common iliac artery and vein could not have been exposed without unduly prolonging the operation, and so the sheath of only the external iliac vessels was split down to a point a little below the inguinal ligament. The operation was completed by loosely closing the peritoneum.

The result was dramatic. On the day following, the patient felt the tension lessen decidedly, and within three days the swelling had gone down remarkably. At a second stage, the femoral sheath was opened in

Scarpa's triangle and Hunter's canal. It is doubtful whether this part of the operation was necessary. Certainly it would have been better to have substituted decompression of the common iliac sheath. But, at least, exploration of the thigh showed that the most active seat of the disease was *above* the inguinal ligament and that it died out in intensity as it descended toward the knee. As a first attempt, this operation can perhaps be considered a success. Some two weeks after the first stage, the swelling, which bade fair to last for many weeks or months, had disappeared, yet in some degree it has since returned, that is, since the patient has gone about again, perhaps because of the incompleteness of the iliac decompression.

One other patient, suffering from a more chronic though less severe disease, has been treated in a similar way, and from this second experience it must be concluded that if the operation is to be of any value, it must be done early; for on this occasion the whole sheath has been converted into a nearly solid scar. The artery was shrunken, in a state of spasm, the vein the less involved of the two vessels. It almost seemed as if the dissection left more damage behind than it relieved. Whether a safe and useful procedure can be devised for opening the sheath from the highest point involved down to the saphenous opening—obviously the most important area—is not yet clear. But at least operation can be said to have revealed the quality of the local process, that is, *a nonsuppurative inflammation marked by a vascular exudate within the iliac and, to a lesser degree, the femoral arteriovenous sheath, affecting artery and vein alike.*

A little more light is shed upon the nature of phlegmasia alba dolens by two other recent observations. If it is a disease of lymphatics, capable of affecting the artery within the common sheath quite as much as the vein, some evidence of arterial disorders, over and above those already described, ought to be forthcoming. During the past winter, a man, forty-three years of age, entered the medical service of the Brigham Hospital suffering from pneumonia. He was not particularly ill, but for some reason was given a hypodermoclysis in the outer part of the right thigh. There remained locally, after what had seemed a normal absorption of the saline solution, a small tender lump, and ten days after the infusion, a slight, tender swelling of the femoral and lower iliac lymph nodes appeared. At the same time, the patient suffered a moderately severe pain in the right thigh, which, within twenty-four hours, was followed by moderate edema of the entire leg. Naturally, it was decidedly interesting to see an instance of phlegmasia alba dolens quite clearly of lymphatic origin,* but it was even more fascinating to

*A somewhat similar case was reported, in 1807, to the Massachusetts Medical Society, by Edward Wyer.[15] At the onset of phlegmasia alba dolens, ten days after childbirth, acute swelling and pain in the lymph nodes at the groin and a streak the color of raspberry juice passing up the front of the leg were noticed. Wyer held the disease to "depend upon an accumulation of lymph in the limb . . . . dependent on causes peculiarly connected with the puerperal state."

discover that the femoral pulse on this side was nearly obliterated and that no pulsations could be felt below the groin. In attempting to take the blood pressure at the popliteal space, one or two arterial beats were heard to come through the cuff at the same pressure as was present in the opposite leg; which makes it clear that the vessel on the affected side was still patent though much narrowed. If this observation is acceptable, it may be believed that the initial pain of milk-leg, which often is so severe as to suggest arterial occlusion, is, in fact, due to an ischemia of arterial origin. Certainly the artery is contracted when seen in explorations of the acute disease. And unless an earlier observation is erroneous, it may even be obliterated. Is it too wild a suggestion to hint that the instances of gangrene which have been reported in the past as complications of typhoid fever and of pneumonia may really have been due to violent arterial spasm or even thrombosis, that is, arterial exhibitions of a state which, in its common form, would be plegmasia alba dolens? Doubtless the arterial side of the disease can readily be observed if only one looks for it.

There is yet one more matter bearing on the nature of phlegmasia. If the characteristic edema is not due primarily to thrombosis within the iliac vein but to a reaction within the arteriovenous sheath, it should be shown that infiltration of this sheath without thrombosis is capable of causing a typical edema. As to this there is actually some clinical evidence. A patient who was operated upon at the Brigham Hospital for biliary obstruction and who died of hemorrhage, happened to have bled into the retroperitoneal tissues of the left pelvic brim. Blood infiltrated the arteriovenous sheath, causing a well-marked edema of the entire corresponding leg, yet without any thrombosis within the vein.

But even more authoritative observations as to the effect of perivenous inflammation in causing swelling of a leg have been recorded by Leriche,[11] and by Leriche and Jung.[12] They made injections of salicylate of soda (30 to 40 per cent solutions) not only into the lumen of the iliac and femoral veins but also into the adventitial sheath about them. In either case, a severe perivenous reaction followed and extensive edema usually occurred. They conclude that occlusion of the veins has little or nothing to do with the result, that perivenous inflammation has everything to do with it and that involvement of vasomotor nerves causes the edema. It seems more reasonable to suppose that involvement of the lymphatics rather than vasomotor fibers is responsible, but doubtless Leriche would say that I had assumed the rôle of the devil and was quoting scripture for my own purposes.

Such, in brief, is the information which bears upon the nature of phlegmasia alba dolens. Are its exhibitions due fundamentally to thrombosis and an inflammatory reaction within the principal vein draining the limb, that is, a primary thrombophlebitis? All of its aspects cannot be explained in this way, and the evidence supporting this

hypothesis is chiefly traditional. Is it due, on the other hand, to a deep lymphangitis, which secondarily affects the blood vessels occupying the same sheath? The evidence strongly favors this hypothesis, even though the source of infection is not usually evident. And here this aspect of the matter must be left for further study. One might suppose that a primary deep lymphangitis within the pelvis could arise in various ways: from the uterus, from the rectum and sigmoid flexure, from the prostate, seminal vesicles and bladder, and of course from the leg itself, as in the instance cited. In any case, all infections taken up by the lymphatics of the pelvis or the legs have direct access to and *must indeed necessarily pass through the great lymph vessels about the external and common iliac blood vessels.* Here, certainly, is the seat of the lesion obstructing the lymphatics draining the leg.

But it must not be taken for granted that the venous side of the disease can be neglected. Venous thrombosis must inevitably be a part of it. The great white swollen leg shows at least a slight cyanosis, and, as the edema recedes, this becomes increasingly evident. If the thrombosis extends down to the popliteal space, there are usually visible dilated anastomotic vessels about the knee joint. And, unless the principal vein is soon recanalized, the anastomotic veins, particularly those connecting the saphenous system with the superficial veins of the abdominal wall, become permanently enlarged, perhaps varicose. In some few cases, both legs are involved, though unequally, as shown in Fig. 3, but whether or not a bilateral process implies that the lower part of the vena cava is affected seems not to be known.

Embolism is, on the whole, unusual. It appears less likely to occur in the course of an outspoken plegmasia alba dolens than from obscure sources of thrombosis near an operative field. That is, perhaps, consistent with the idea of a perivenous inflammation causing a secondary clot in the iliac vein, for such a clot, except perhaps in the presence of suppurative sorts of infection, would be likely to have a uniform character, unlikely to undergo a septic softening, and would be solidly adherent to the vein's wall. In most instances, then, fear of embolism need hardly militate against any proposed treatment.

The treatment of phlegmasia alba dolens ought to be planned to get rid of the edema at the earliest moment, to restore the lymphatic circulation and to forestall the late complications. There is no reason, at an early stage, for doing anything but giving such opiates as are needed and elevating the leg. There is every reason for not using ice on the leg, for the basic lesion is not there, and even if it were, ice would be the worst possible remedy for it.

As soon as fever has disappeared and tension has lessened a little, the leg should be exercised in bed, first by setting and relaxing the muscles and then by actually moving it. There is no objection, even, to light massage. Such measures are no more liable to cause embolism than taking a

bed-bath or using a bed-pan. As the swelling goes down, the patient should begin to exercise the leg in a dependent position—the main thing being *never* to let it remain dependent except when exercising it. For the more readily lymph is drained from the limb and the fewer hours out of each twenty-four the tissues are kept soaked in lymph, the less liable are secondary infections to occur. The late complications and their treatment have already been described. It is clear that only when lymphstasis is superficial and local, can efforts to drain lymph from the superficial tissues into the deeper parts by the Kondoleon procedure have any success. To attempt such an operation in the face of generalized lymphstasis in the leg, due to plugging of the principal lymph vessels above the groin, is utterly unreasonable.

Operative treatment of phlegmasia alba dolens is in the experimental stage. It should only be used upon the worst cases and should probably be confined to splitting the sheath over the iliac vessels. There is no doubt that, if performed promptly, it causes the swelling to recede in a remarkable way, but whether an abdominal operation should be added to the patient's difficulties is not yet clear. Evidently, since the obstruction is primary about the great iliac vessels, there and not elsewhere is the place to attack. Yet the operation requires some degree of skill, and since it entails, in the treatment of a disease not in itself fatal, a possible risk to life, it must be shown to have decided advantages before it can be accepted even as a basis for further progress.

To recapitulate, there are forms of thrombophlebitis dependent upon an unhealthy state of the vein's wall—the varicose type—and peculiar sorts, partly of local origin and partly due, perhaps, to an abnormality of the blood—phlebitis migrans. There are also venous thromboses of traumatic origin. But thrombophlebitis which affects the previously healthy veins draining the lower limbs, particularly the familiar scourge, phlegmasia alba dolens, appears to be secondary to a nonsuppurative lymphangitis, which from its situation, is able to attack artery as well as vein. And the principal exhibitions of such a disease are neither venous nor arterial, but lymphatic.

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SOME CLINICAL FEATURES OF CORONARY ARTERY DISEASE*†

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IT WAS Edward Jenner,[1] in the latter part of the eighteenth century, who first suggested the probable relationship between calcareous deposits in the coronary arteries and that "disorder of the breast" to which his contemporary, Heberden, gave the name "angina pectoris." With Jenner's observations, followed soon after by those of Parry, originated the concept that there was an association between disturbances in the coronary circulation and the manifestations of a disordered heart. In 1884, Leyden[2] gave an excellent description of coronary sclerosis and thrombosis, and for the first time satisfactorily correlated symptoms, signs and pathological changes. The evolution of sharply delineated clinical pictures has been slow, though stimulated during the past twenty years by renewed interest in acute coronary obstruction. In the development of our knowledge concerning this condition, the paper of the Russians, Obrastzow and Straschesko[3] in 1910, and the publications of J. B. Herrick[4] in 1912 and 1919, will stand, together with Leyden's account, as historic landmarks.

What are the various affections which may involve the coronary arteries? Data on this point have been obtained from the autopsy records of the Presbyterian Hospital covering the ten-year period 1920

TABLE I

ETIOLOGIC TYPES OF CORONARY DISEASE WITH ASSOCIATED PATHOLOGIC STATES.* THEIR RELATIVE FREQUENCY IN 148 AUTOPSIES AT THE PRESBYTERIAN HOSPITAL, NEW YORK (1920 TO 1929, INCLUSIVE)

1. Arteriosclerosis	
a. Atheroma b. Calcification c. Stenosis d. Occlusion	110
e. Thrombosis	22
f. Infarct of myocardium	56
g. Aneurysm of heart	5
h. Rupture of heart	3
2. Syphilis	
a. Stenosis or obliteration of orifice	12
b. Infarct of myocardium	3
3. Rheumatic fever	
a. Arteritis	2
4. Embolism	1
5. Periarteritis nodosa	
a. Arteritis	1

*Obviously, in a number of instances, more than one lesion was present.

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to 1929, inclusive.* During this time, 148 cases (10.7 per cent of all the autopsies) showed lesions in the coronary vessels. The etiological types of pathological condition observed, together with their relative frequency, are shown in Table I.

Syphilis of the coronary arteries is seen almost exclusively in association with specific aortitis, and assumes clinical importance when the orifice of one or both coronaries becomes stenosed or obliterated. In such cases, as pointed out by von Glahn,[5] the abnormally high origin of the vessels predisposes to their involvement by the syphilitic process in the aorta. Syphilitic arteritis of the smaller intermuscular branches, described by Warthin,[6] was not encountered in this series; nor was coronary involvement found in cases of thromboangiitis obliterans or erythremia. The coronary lesions of rheumatic fever, for the present, are of interest chiefly to the pathologist. Clearly, the arteriosclerotic group, with the concomitant morbid changes in the heart, is numerically by far the most important. The relatively high incidence of infarction of the myocardium unassociated with recent thrombosis, is noteworthy. Some of these infarcts no doubt are the result of an old, acute thrombotic occlusion. Many, however, appear to follow the more gradual closure of a branch, due to sclerotic changes.

The infrequency of embolism of a coronary artery also deserves mention. In a series of 3093 autopsies performed in the course of twenty-four years, this condition was met with but three times. It occurred once in a young man with vegetative endocarditis of the aortic valve, who died suddenly due to the plugging of the orifice of the left coronary by a piece of vegetation. A second instance was observed in a boy of nineteen years, who suffered from subacute mitral and aortic endocarditis due to Bacillus influenzae. The coronary embolus was small and death was gradual. The third case was that of an eighteen-year-old boy, who died suddenly after an enema. The myocardium showed a curious hydropic degeneration, with fibrosis and infarction. There were thrombi in the right ventricle, and an embolus was found in the anterior descending branch of the left coronary artery.

That heart disease is now the leading cause of death, and that its mortality curve has been rising steadily for the past twenty years is a matter of common knowledge. But that the increasing number of deaths from diseases of the heart occurs almost entirely in persons over the age of forty-five years, is not so generally appreciated.[7] In the younger age groups, the rate is actually falling. How is the increasing number of cardiac deaths in older individuals to be explained? It is due, in large measure, to the fact that more people are living to the "heart age," that is, they survive to that period of life when degen-

*The period was begun with the year 1920, because by this time the various features of coronary artery disease were sufficiently well known to make valid a comparison between autopsy and clinical records. The period was terminated with the year 1929, because of re-arrangement of the hospital service after this date. Subsequent figures, therefore, were not comparable. I am indebted to Dr. James W. Jobling for permission to utilize the Records of the Department of Pathology.

erative processes affect the circulatory system to a sufficient degree to cause functional impairment. In addition, the growing body of knowledge concerning cardiovascular conditions has resulted in more accurate diagnosis. We are becoming increasingly familiar with the protean manifestations of circulatory disorders, and it is now rare to find the cause of death given as "acute indigestion" or "senility."

The question naturally presents itself as to whether affections of the coronary arteries are likewise showing a rising trend in their incidence. Again, the autopsy files of the Presbyterian Hospital were consulted, using the material recorded during the ten-year period 1920 to 1929, inclusive. The results of the analysis are shown in Table II. It is apparent that, although the percentage of cases of coronary disease in relation to the total number of autopsies has shown some variation from year to year, yet there has been no distinct trend either up or down. In both 1920 and 1929, the figure was 12 per cent. The evidence presented by this particular group of cases affords no support for the current impression that an increasing proportion of the population is dying of coronary artery disease. No other comparable set of figures has been published. Before drawing a general conclusion, it will be necessary to analyze a large and assorted material.

TABLE II

PERCENTAGE OF CASES OF CORONARY ARTERY DISEASE* IN RELATION TO TOTAL NUMBER OF AUTOPSIES, 1920 TO 1929, INCLUSIVE (PRESBYTERIAN HOSPITAL, NEW YORK)

YEAR	TOTAL NO. OF AUTOPSIES	NO. OF CASES OF CORONARY DISEASE	PERCENTAGE OF CASES OF CORONARY DISEASE
1920	124	16	12.9
1921	91	12	13.2
1922	147	13	8.8
1923	123	7	5.7
1924	127	13	10.2
1925	118	14	11.9
1926	144	20	13.9
1927	115	13	11.3
1928	151	11	7.3
1929	240	29	12.1
Total period	1380	148	10.7

*Anatomical diagnoses included are: arteriosclerosis of coronary artery, thrombosis of coronary artery, embolism of coronary artery, syphilitic stenosis or obliteration of orifice of coronary artery, infarct of heart and aneurysm of heart. Cases filed under more than one heading are counted only once.

The clinical diagnoses during the same ten-year period were then tabulated for comparison with the autopsy findings (Table III). The analysis was based upon the percentage of cases diagnosticated as coronary artery disease, in relation to the total number of admissions to the medical service. The difference in trend is striking, for with minor fluctuations, the percentage rises from 1.1 in 1920 to 4.3 in 1929—a fourfold increase. Tabulation of the cases by age groups showed that

the increase in the latter part of the period was not due to the fact that during these years a greater number of elderly patients was admitted to the hospital.

How can this discrepancy between autopsy and clinical records be reconciled? I believe that the explanation can be stated briefly and in modern parlance. Thus, it may be said that during the last two decades we have grown to be "heart-minded"; in the past ten years we have become "coronary-conscious." Many of the milder, nonfatal and atypical forms of coronary disease are being recognized with increasing frequency. For this reason, the figures for the later years probably more nearly approximate the truth.

TABLE III

PERCENTAGE OF CASES DIAGNOSED AS CORONARY ARTERY DISEASE* IN RELATION TO TOTAL NUMBER OF ADMISSIONS TO MEDICAL SERVICE, 1920 TO 1929, INCLUSIVE (PRESBYTERIAN HOSPITAL, NEW YORK)

YEAR	TOTAL NO. OF MEDICAL ADMISSIONS	NO. OF CASES OF CORONARY DISEASE	PERCENTAGE OF CASES OF CORONARY DISEASE
1920	1886	20	1.1
1921	1837	17	0.9
1922	1820	19	1.0
1923	1587	13	0.8
1924	1677	35	2.1
1925	1720	33	1.9
1926	1639	47	2.9
1927	1651	38	2.3
1928	1581	58	3.7
1929	2198	94	4.3
Total period	17,596	374	2.1

*Clinical diagnoses included are: arteriosclerosis of cornary artery, thrombosis of coronary artery and infarct of heart. Cases filed under angina pectoris are also included if the record suggests that coronary diesease was the basic pathologic state.
•Cases filed under more than one heading are counted only once.

It has been pointed out that arteriosclerosis, with the various associated lesions in the myocardium, is the commonest form of coronary affection. We apply to it the name of disease because there is an ill-defined transition zone between those changes incident to the normal processes of senescence and the morbid states which are regarded as pathological. For clinical purposes, it may be said that disease exists when the degenerative process has induced alterations in a tissue or organ in such a manner or in such a location that symptoms and signs of functional impairment become manifest. Usually, coronary sclerosis is part of a generalized arterial degeneration; occasionally, only the coronary bed appears to be involved to a significant degree.

Concerning the causes which predispose to degenerative changes in the coronary vessels but little is known. Heredity undoubtedly plays a rôle, for several members of a family may suffer from the anginal syndrome and die in the agony of an attack. As Osler phrased it, "in the make-up of the machine, bad material was used for the tubing."

Men are more frequently affected than women. Evidences of impairment of function usually appear after the age of forty, and the fifth may well be called the dangerous decade. The part played in etiology by diet, by infections, general and focal, as well as by tobacco, alcohol and endocrine imbalance, is not clearly defined. In patients with diabetes mellitus, coronary disease is encountered with relative frequency.[8] Obesity, especially in the hypertensive, undoubtedly places an added burden on the circulation; and hypertension itself often precedes, or accompanies atheroma. Warthin's[6] contention that syphilis predisposes to coronary sclerosis and its resultant cardiac pathology, finds no support in the observations of others.[9] There is much current talk concerning the specific deleterious effects of the hurry, worry and speed of modern life upon the cardiovascular system. It is difficult to prove such a relationship, for many factors must be taken into account. And it is well to bear in mind that arteriosclerosis is a disease of antiquity, found in the mummied corpses of Egyptians who lived 3500 years ago. The cause of truth is not furthered by drawing hasty and ill-founded inferences based upon circumstantial evidence.

The pathological changes in the heart which result from sclerosis of the coronary arteries will, of course, vary according to the extent and location of the vascular lesions. Small isolated plaques may cause no damage to the myocardium. Impairment of the circulation of the heart muscle may result in patchy fibrosis. Stenosis and occlusion are often followed by the formation of an infarct, and if the area of softening and subsequent thinning of the wall is extensive, aneurysmal dilatation of the ventricle follows. If the changes are diffuse, the heart enlarges, chiefly by hypertrophy. It is axiomatic that an enlarged heart is a diseased heart, though not necessarily one which is functionally inadequate.

It has been pointed out by Gross[10] and by Oberhelman and Le Count[11] that there are wide variations in the distribution and anastomoses of the coronary arteries, in different individuals and at different periods of life. It is reasonable to expect, therefore, that the manifestations of disturbances in the coronary circulation will be variable, due in part to anatomical conditions, and in a measure to other individual constitutional factors. Clinically, the cases of coronary sclerosis (exclusive of thrombosis) may be divided, according to their presenting symptoms, into four groups: (1) those with cardiac insufficiency; (2) those with cardiac pain; (3) those with digestive disturbances; (4) those without symptoms, and sometimes without signs —the latent type. Obviously, there are many mixed cases with symptoms from more than one group.

(1) *The heart failure group.* A majority of the cases which were formerly called "chronic myocarditis," and to which the term "fibrosis of the myocardium" is now applied, are the result of sclerotic changes

in the coronary arteries. Frequently it is the smaller branches which are involved. The heart is usually enlarged. Hypertension is sometimes, though not necessarily, present. The patients are most often men in the fifth or sixth decades of life. Signs of valvular disease are usually absent, but an apical systolic murmur may be heard, sometimes due to a flabby and dilated mitral ring. Anatomical mitral insufficiency may result from extension of the sclerotic process from the aorta to the anterior cusp of the mitral valve; a similar atheromatous or calcified lesion may deform the aortic valve segments, with the production of leakage or narrowing at the aortic orifice.

The symptoms of cardiac insufficiency are insidious in their onset. Slight dyspnea after a degree of effort which was habitually unattended by discomfort, is an early harbinger of trouble. Swelling of the ankles above the shoe tops, toward evening, follows ere long. Cough, a sense of fullness in the epigastrium, due to a swollen liver, and inability to recline comfortably in bed on the customary number of pillows, are later evidences of advancing heart failure. Tachycardia and irregularity of the heart's action, in the form of premature beats or auricular fibrillation, may cause the patient to complain of palpitation. I have been particularly impressed by the frequency with which premature beats of auricular origin are observed in these cases. Heart-block, partial or complete, is one of the forms of arrhythmia more rarely encountered. Changes in the form of the electrocardiogram, if present, afford confirmatory evidence of myocardial fibrosis, and their character may be of decided aid in estimating the severity of the cardiac damage. Often, however, the graphic record shows little or no deviation from the normal, in spite of the clinical picture of advanced failure.

Once the signs of myocardial insufficiency have appeared, the course is usually progressively downward. Each successive break in compensation is followed by slower and less complete recovery. Arteriosclerotic closure of a coronary branch, if gradual, may be unattended by symptomatic disturbance. If the obstruction of the lumen is sudden, discomfort is often marked. As in thrombotic occlusion, there may be pain, nausea, vomiting and occasionally transitory cardiac irregularity due most frequently to premature beats or auricular fibrillation. If the obstructed vessel is of fair size, there is formed an infarct of the myocardium. Subsequently, aneurysmal dilatation of the ventricle may develop. In the late stages of failure, paroxysms of nocturnal dyspnea (so-called cardiac asthma) are not uncommon and may be accompanied by pulmonary edema. Yet, with careful management, some of these patients are able to carry on at a lowered level of activity for a number of years. The end may come gradually, from increasingly severe heart failure, or quickly, from acute coronary obstruction or a cerebral hemorrhage. If the kidneys are affected, uremia is sometimes the terminal event.

(2) *The pain group.* The cases characterized by attacks of substernal or precordial pain are commonly called by the generic term "angina pectoris." On previous occasions, I have endeavored to point out the undesirability of applying to this symptom a designation which, historically at least, carries with it the implication of a particular disease.[12] Pain in the chest may be an expression of a number of basic pathological states. It is profitable and indeed, essential, to consider the diagnostic problem from its etiological, anatomical and functional aspects, if intelligent therapy is to be given and a reasonably accurate prognosis is to be attempted.

The mechanisms by which pain impulses originate in the heart and are transmitted from it to distant points of reference, are as yet but imperfectly understood. It would require too much time to give them adequate consideration here. It is sufficient to say that there is increasingly convincing evidence, both clinical and experimental, which indicates that heart pain, paroxysmal or prolonged, is usually of coronary origin and results from myocardial ischemia.[13] In a study of the pain in intermittent claudication, Lewis[14] has recently shown that chemical or physicochemical factors are also concerned in its production. As he has indicated, analogous conditions may prevail in pain of cardiac origin. Furthermore, transient changes in the form of the electrocardiogram during brief attacks strongly suggest the possibility that the anoxemia is in part functional and in such paroxysms may arise from spasm of the coronary arterioles.[15]

The characteristics of what may be called a typical attack are well known. The pain may occur not only after effort or emotion, but at rest, and not infrequently at night, in bed. It varies in intensity, in part according to the sensitivity of the individual to painful stimuli. A sense of substernal oppression may be as significant as the sharpest twinge. There are many equivalents of breast pang, such as headache, dizziness, a sudden feeling of great weakness, sweating (sometimes unilateral in distribution), nausea or vomiting.[16] An unusual opportunity to observe the substitution of paroxysms of dyspnea for pain was afforded recently. A man, aged forty-four years, with coronary sclerosis and attacks of pain so severe that he had been completely incapacitated for eight months, received paravertebral injections of alcohol into the first five dorsal rami two and one-half years ago. He was completely relieved of the paroxysms and was able to return to work. He came to the clinic three weeks ago, complaining of attacks, occurring both after effort and at rest, during which he became suddenly short of breath and actually gasped for air. The attacks were accompanied by an aching sensation in the left elbow. All discomfort was promptly relieved by nitroglycerine. Such pain equivalents are frequently confusing and I believe are often present in patients who die suddenly and who are said to have had no previous cardiac complaints.

(3) *The digestive group.* It is only in recent years that adequate emphasis has been placed upon the importance of digestive disturbances as part of the picture of myocardial disease. Both the gastrointestinal tract and the heart are innervated by large branches of the vagus nerve, so that reciprocal symptoms might well be anticipated. There are, in addition, numerous intercommunicating sympathetic pathways. Indigestion is one of the favorite disguises of coronary sclerosis; flatulence and belching are among its common manifestations. Many of these patients are treated for supposed ailments of the stomach, bowel or gall bladder. A paroxysm of cardiac pain may be referred entirely to the epigastrium; nausea and vomiting attract further attention to the abdomen as the source of trouble. The more violent digestive symptoms in acute coronary obstruction are of even greater interest and importance; reference will be made to them again under that caption.

(4) *The latent group.* It is hardly necessary to point out that the presence of coronary sclerosis is frequently overlooked during life and is found as a surprise at the post-mortem table. In a series of 86 consecutive, proved cases studied by Willius and Brown[17] at the Mayo Clinic, 34, or 40 per cent were of the latent type, in which there was insufficient subjective or objective evidence of cardiac disease to permit of its clinical identification. Coronary disease should be suspected whenever a chronic, nonvalvular affection of the heart is observed in an individual over forty years of age. Attention paid to the atypical manifestations will result in a higher percentage of correct diagnoses.

Thrombosis of a coronary artery may be considered as an episode in the natural history of coronary sclerosis, for the thrombus almost invariably forms in a vessel already the seat of atheroma or calcification. So, in a majority of instances, if a careful history is taken, or a complete examination is made prior to the attack, some evidence of previous cardiac disturbance will be discovered. The dramatic features of sudden obstruction of a large coronary branch impress themselves indelibly upon the memory of the observer. The agonizing and prolonged substernal or epigastric pain, the nausea, vomiting and belching of gas, the ashen countenance bathed in cold sweat, and the anxiety of the sufferer, all serve to define a picture which is now well known.[18] The blood pressure falls, the heart rate rises, and cardiac arrhythmias of various types may appear. The presence of a gallop rhythm indicates that the myocardium has been severely damaged.

Following the shutting off of the blood supply to an area of heart muscle, an infarct develops, varying in size with the caliber and number of occluded branches. If the infarct reaches the pericardial surface, a friction rub may be audible, often only for a short time. Necrosis of the myocardium is followed, after the lapse of some hours, by fever. The leucocyte count rises, at times soon after the occlusion, and may

be as high as 30,000. Almost invariably, even in the absence of leucocytosis, there is relative polynucleosis. Persistence of fever and leucocytosis for a number of days, or a rise in either or both, is strongly suggestive of progressive myocardial necrosis or intracardiac thrombosis.[19] Bits of thrombus within the ventricle may become detached, and depending upon whether the right or the left side of the heart is the site of infarction, emboli may be carried to the lungs or systemic circulation. Hemoptysis due to pulmonary infarction is relatively frequent; hemiplegia and the plugging of an artery in the leg are graver complications.

The electrocardiogram is often of great aid in differential diagnosis and is useful in following the progress of the cardiac lesion.[20] To consider it in detail is not within the scope of this paper. Three points should be kept in mind in the interpretation of the records: (1) form changes, if present, should not be regarded as etiologically specific; (2) successive changes from day to day, or week to week, afford evidence of altering conditions in the myocardium, and may indicate healing of the infarct or an advancing lesion; (3) a relatively normal record may be obtained, even though there is extensive damage to the heart muscle.

Much attention has been directed to the abdominal symptoms of coronary thrombosis, for they have led to great confusion in diagnosis. The acute cardiac upset has been mistaken for cholecystitis, cholelithiasis, acute pancreatitis, perforated gastric or duodenal ulcer, intestinal obstruction and hemorrhage into the suprarenal capsule. Surgical procedures have actually been attempted under these circumstances. So strongly have the abdominal manifestations of a coronary attack been impressed upon the minds of physicians, that there is now a tendency for the diagnostic pendulum to swing in the opposite direction. A case in point is as follows:

CASE REPORT

Mrs. B., aged 61 years, was a widow. One brother had died of heart disease. She had had no severe illnesses and physically was very active. She could climb stairs and hills, and worked in her garden without discomfort. The digestion was usually good.

One evening, she dined in the restaurant of the apartment hotel in which she lived. She was awakened at 2 o'clock the following morning by severe abdominal cramps, followed by profuse vomiting. The pain did not radiate to the arms or chest. The house physician was summoned, and greatly alarmed her family by stating that the symptoms were due to a heart attack resulting from acute coronary obstruction. Later in the morning, she was seen by her family doctor, who found her very weak but free from pain. The systolic blood pressure, which was usually about 125, had fallen to 110 mm. Hg. There was no fever. She remained in bed for several days and when I saw her two weeks later, felt very well.

Examination at that time showed slight sclerosis of the retinal arteries, but no thickening of the peripheral vessels. The heart was not enlarged either on per-

cussion or on fluoroscopic examination. The rhythm was regular. The sounds were of moderate intensity. There was a faint systolic blow at the apex and at the aortic area. The blood pressure was 142 mm. Hg systolic; 86 diastolic. The aorta was not dilated and its pulsations were quite vigorous. The electrocardiogram showed left axis deviation, but no other changes. In short, there were no signs of cardiovascular disease except for the moderate amount of arteriosclerosis, to which the patient, at her age, was entitled. It was thought that the attack of abdominal pain and vomiting was probably due to food poisoning. On further inquiry, it was found that three other women, who had eaten the same table d'hôte dinner in the same restaurant on the same evening were similarly affected, though they were less violently ill. The patient has been perfectly well during the past six months.

In this case, then, the symptoms of a gastrointestinal upset were attributed to acute coronary obstruction. Detailed examination revealed no evidence of heart disease, and the subsequent course has borne out the impression that the attack was not of cardiac origin.

There are mild and atypical cases, many of which are undoubtedly overlooked. A sense of substernal oppression, a mild twinge of pain, a paroxysm of dyspnea, an aching sensation in the arm or a sudden feeling of great weakness may indicate acute obstruction of a coronary twig. There may be slight fever and leucocytosis. The inference that such symptoms truly represent a thrombotic closure is often borne out by serial electrocardiographic studies in which successive changes appear in the records; or by the occurrence, months or years later, of a more severe and perhaps fatal attack. A group of such cases has recently been reported in detail.[21] An illustrative instance is as follows:

CASE REPORT

Mr. W., aged 66 years, was a business executive. One brother had died at the age of 60, of heart disease. He had never been seriously ill, nor had there been any cardiac symptoms.

The present illness began two weeks before his visit. While playing golf, he suddenly experienced a sense of pressure over the sterum, but no pain. This lasted ten or fifteen minutes, and he was able to finish the round. A week later, while coming out of a theater, the same sensation recurred, not severe, but lasting about an hour. He broke out into a profuse perspiration. On the following day, while in bed, he noted tingling in the left arm and substernal pressure, again lasting about an hour, and accompanied by sweating about the head, neck and chest. He recalled that he was obliged to change into a fresh pair of pajamas. A similar "cold sweat" occurred on the next night. At no time was there any pain, and he went to business regularly.

On examination, the patient appeared to be at least ten years younger than his stated age. The heart, by percussion, was moderately enlarged to the left. The rhythm was regular; the rate 68. The sounds were quite weak, but no gallop rhythm was heard. The blood pressure was 130 mm. Hg systolic; 86 diastolic. On fluoroscopic examination, cardiac enlargement was confirmed, and the aortic knob was found to be prominent.

An electrocardiogram was made by another physician ten days after the onset of symptoms. This showed regular sinus rhythm and slight left axis deviation. The T-wave was inverted in Lead I, and upright in Leads II and III. Another record, taken three days later, showed striking changes. T_1 was now upright. There

was slight elevation of the R-T interval in Lead I, and marked elevation in Lead II. There was no disturbance in conduction.

It was thought that the patient had had occlusion of a small coronary branch, and that the sense of substernal pressure and sweating appeared as substitution symptoms in place of pain. He was kept in bed for three weeks. There was no recurrence of discomfort. During the following four months, numerous electrocardiograms were taken. T_1 became progressively higher and the elevation of the R-T interval in Leads I and II disapepared. These successive changes in the electrocardiograms were due, it was believed, to alteration in the state of the myocardium, associated with healing of a small myocardial infarct.

This case exemplifies one of the mild forms of coronary thrombosis without pain, in which a sense of substernal oppression was accompanied and followed by profuse sweating. Recovery was rapid, but the successive changes in the electrocardiogram afforded definite evidence of injury to the heart muscle.

Coronary thrombosis may cause almost instantaneous death, probably due to fibrillation of the ventricles. Some patients live for a few hours, others for days, months or years. Following recovery from an acute attack, life may terminate gradually, with signs of cardiac insufficiency, or suddenly, due to a fresh obstructive lesion. Occasionally, the heart wall, weakened by a large area of necrosis, ruptures. If the infarct heals and is replaced by an extensive fibrotic scar, an aneurysm of the ventricle may develop.[22]

In a series of 287 cases analyzed by Conner and Holt,[23] the immediate mortality in the first attack was 16 per cent. Among the patients in their group having two or more attacks, the time interval between the first and second attack was less than one year in half the cases. One patient remained in good health for seventeen years and died in a second attack eighteen years after the first. Mild initial symptoms and a rapid rate of recovery tend to indicate a favorable immediate outcome. But in any given instance, it is extremely difficult to prognosticate as to the liability to recurrence, or to estimate the probable expectancy of life.

A presentation such as this is necessarily fragmentary and incomplete. I shall take comfort from the words of Oliver Wendell Holmes,[24] who, in a lecture delivered at the Harvard Medical School in 1867, gave this advice to the junior members of the faculty: "Do not fret over the details you have to omit; you probably teach altogether too many as it is."

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THE OPENING SNAP (*CLAQUEMENT D'OUVERTURE DE LA MITRALE*) IN MITRAL STENOSIS, ITS CHARACTERISTICS, MECHANISM OF PRODUCTION AND DIAGNOSTIC IMPORTANCE*†

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IN MOST patients with mitral stenosis a characteristic snapping or clicking sound occurs shortly after the second heart sound. It is sometimes audible over the entire precordium. It is usually heard best in the fourth left interspace and occasionally may be louder in this position than either the first or second sound. In spite of the fact that the sound has been clearly described a number of times, it seems never to have gained the recognition merited by its diagnostic significance. It has been confused by most writers either with reduplication of the second heart sound or with gallop rhythm. Reduplication of the second sound is frequently present in mitral stenosis but has practically no diagnostic importance, since it is often found in undamaged hearts and in various types of heart disease other than mitral stenosis. It is questionable whether gallop rhythm ever occurs in the presence of well-developed mitral stenosis. The sound, however, to which we wish to recall attention does help to produce a *grouping* of sounds not very different from that of protodiastolic gallop rhythm. However, it resembles gallop rhythm in no other of its physical characteristics and may be readily differentiated from it.

Duroziez[1] in 1862 gave the first recognizable description of this third sound as a part of the pathognomonic sound rhythm of mitral stenosis (which he represented by the syllables ffout-ta-ta-rou), but he, and later Potain[2] ascribed it to asynchronism in aortic and pulmonic closure. Guttman[3] was the first to recognize that the sound is not due to reduplication at the base. He made the important suggestion that it originates at the stenosed mitral orifice itself; although he stated erroneously that it is most clearly heard over the lower part of the sternum or near the apex of the heart. In 1881 the sound was described for the first time in the English literature by Sansom,[4] who adopted Guttman's view that it is produced at the mitral orifice. He believed that the cause of the sound is tension on the "mitral curtains." Sansom invented the term "reduplication of the second sound at the apex," which unfortunately persists.

In 1888, Rouches,[5] whose interest had been stimulated by Potain, pub-

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†Presented in part before the American Climatological and Clinical Association, Quebec, Canada, May 13, 1930, under the title "The Early Diastolic Snap (Claquement d'ouverture de la mitrale) in Mitral Stenosis."

lished a thesis on the subject. He characterized the sound as a sharp snap heard in mitral stenosis with or without associated insufficiency, coming shortly after the second sound and marking the beginning of the diastolic rumble. He called the sound *Le claquement d'ouverture de la mitrale,* stating that Potain had used this term in his teaching.* Among Rouches' conclusions were the following: (1) the active cause of the *claquement d'ouverture de la mitrale* is stretching of the stenosed valves by the pressure of blood unable to flow freely from the auricles; (2) the sound does not occur if the valve leaflets do not retain some suppleness and ability to snap when stretched; (3) the sound therefore denotes the presence of pronounced but not extreme stenosis. Following the contributions of Guttman, Sansom, and Rouches, other papers appeared[6, 7] but added nothing of importance to the observations of these investigators. In 1905 and again in 1912, Gallavardin[8, 9] discussed this sound and attributed it to the effect of a shock-like wave, initiated by aortic closure. He assumed further that this wave traveled downward and struck against a stenosed but open mitral valve. In his second paper, the physiological third heart sound was attributed to the shock-like wave striking a normal open mitral valve. The differences in quality of the sounds were regarded as due merely to the differences in the physical properties of the normal and stenosed valves.

Heart sound registration methods offer an excellent opportunity to study this sound, since it is easily recorded. A search of the literature, however, reveals the fact that very little work has been done in this field. Lewis[10] noted a gap between the second sound and the beginning of the diastolic murmur. Wilson and Wishart[11] also observed a pause between the second sound and the beginning of the diastolic murmur which gave rise to a triple rhythm. Groedel[12] has recently referred to a "splitting" of the second sound and states that the diastolic murmur begins with large vibrations which one can hear as a third sound. These statements can be confirmed by sound registration methods in certain cases of mitral stenosis, but all these writers overlook the snapping sound pointed out by earlier observers. It is true that there is a gap between the second heart sound and the beginning of the diastolic murmur which is revealed by sound tracings if the recording apparatus is sufficiently damped. It is likewise true that the tracings frequently show the murmur of mitral stenosis to be initiated by a series of vibrations of relatively large amplitude. The characteristic third sound of mitral stenosis, however, is neither a part of the second sound nor a part of the murmur. It disturbs the quiet of what would otherwise be an auscultatory gap between the second sound and the murmur.

Recently Mozer and Duchosal[13] have published sound tracings in which they have called attention to the snap (*bruit de rappel*). These workers

*Apparently Potain had come to this conclusion after publishing the paper in 1875 referred to above.

adopted Gallavardin's hypothesis with respect to the mechanism of production of the sound and ascribed not only the physiological third heart sound but also reduplication of the second sound to the same mechanism. These views will be discussed later.

Nomenclature. Of the various designations which have been used to call attention to this characteristic sound in mitral stenosis, Rouches' *claquement d'ouverture de la mitrale* and the corresponding term "opening snap" used by Thayer[14] are the most acceptable. In the earlier part of our work, we were unwilling to adopt this term on the ground that it implied a mechanism of production of the sound which was unproved. Our studies of this mechanism, however, support the view held by the earlier writers that the sound is due to an opening snap of the mitral valve, thus warranting retention of the term. The designation *bruit de rappel* which has been used by certain French writers, although picturesque, has little significance and should be discarded.

Material and Methods of Sound Registration. During the past three years we have made clinical and sound registration studies in 60 cases of mitral stenosis. Some of the cases have been followed throughout most of this time, others for shorter periods. The apparatus which has been used for recording sound includes a three-stage transformer coupled amplifier,* the Western Electric transmitter and output receiver. In the early part of the work, the optical apparatus devised by Wiggers was used.† Because of the limitations of the Wiggers apparatus in recording high-pitched sounds and its imperfect damping quality, at least so far as our ability to use it is concerned, it was regarded as unsuitable to record the snap satisfactorily and to display its time relationships. Consequently the rubber cement membrane and reflecting mirror were attached over the outlet of the output receiver, making possible the use of a smaller membrane with a higher vibration frequency and quicker damping. With this modification,‡ which eliminates one part of the apparatus and therefore one possibility for distortion of sound, the snap is easily recorded and because the sounds are quickly damped their time relationships are clearly displayed. Waves of low frequency are not recorded with as great amplitude as with the Wiggers device, or with the electrocardiographic string, but for our present purposes this is unimportant.

THE FREQUENCY OF THE OPENING SNAP AND ITS CHARACTERISTICS

The sound is audible in the majority of cases of mitral stenosis. We were able to elicit it, both by auscultation and by sound registration

*The amplifier has a frequency characteristic adapted for heart sounds. It was constructed for us by Professor Charles Weyl of the Moore School of Electrical Engineering, University of Pennsylvania.

†Numerous tests were made to determine the adequacy of this apparatus. These have been previously mentioned.[15]

‡This modification of the method will be described by one of us (Margolies) in a separate publication.

methods, in 19 of 34 consecutive cases in which this valve lesion was diagnosed. Its occurrence does not seem to be materially influenced by the presence or absence of associated lesions. Gallavardin[9] failed to elicit the snap when aortic regurgitation was present, and Mozer and Duchosal[13] also failed to find it in two such cases. These authors, therefore, state that aortic regurgitation prevents the occurrence of the snap. This observation was believed by them to have great significance with respect to the mechanism of production of the snap. As a matter of

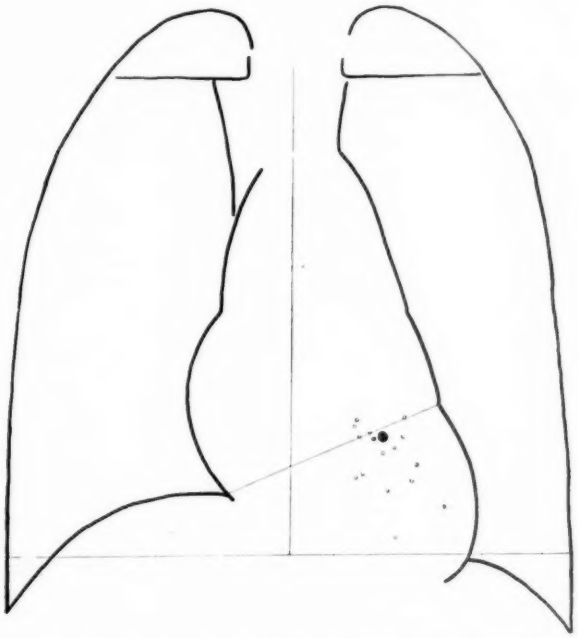

Fig. 1.—The relation of the position of maximum audibility of the opening snap to the basal diameter and the left border of the heart. (See text for description of method.) The large dot represents this position in the patient from whom the orthodiagram was made. The small circles represent this relationship in fifteen other cases. The drawing does not take into account the differences in size, shape and position of the heart in these fifteen cases. For example, the lowest circle was taken from the orthodiagram of a patient with a very large heart in whom the snap was not so close to the apex as its position in this drawing would suggest. The point of maximum audibility is never basal or apical.

fact, the occurrence of the snap is not prevented by the presence of aortic regurgitation. We have studied 4 cases with both mitral stenosis and aortic regurgitation in which the snap could be heard and recorded.

Quality and Intensity. The sound is always short, and usually high-pitched, having a snapping or clicking quality. Its intensity varies. It is frequently loud enough to be audible over the entire precordium. Sometimes it is less distinct and is heard over a limited area only.

Area of Maximum Audibility. The area over which the sound is heard best is usually located in the fourth interspace, just inside the left border

of the heart. Occasionally it is heard best in the third interspace. Fig. 1 is a diagram made in the attempt to illustrate the relation which this point bore to the cardiac silhouette in 16 cases. These data were obtained by determining the position of maximum loudness of the sound by auscultation with a stethoscope. The position was marked by strapping a small piece of lead over it. Its relation to the cardiac shadow was then determined by fluoroscopy. The latter was found to be from 1.5 to 4.5 cm. inside the left border and usually from 0.5 cm. above to 2.5 cm. below the so-called basal diameter.*

The area over which the snap is heard best is slightly above and to the right of the area over which the characteristic diastolic murmur of mitral stenosis is usually most clearly audible. This auscultatory finding is supported by a comparison of the relative amplitudes of the vibrations in sound tracings taken over these two areas (Fig. 2 *A* and *B*).

Transmission. The opening snap does not seem to be transmitted in any particular direction, but if it is loud enough to be heard at a distance, it is sometimes more distinct over the aortic than over the pulmonic area.

Time Relation to the Second Heart Sound. In our cases the snap usually occurred 0.06 to 0.11 second after the beginning of the second sound. The shortest interval recorded was 0.03 second (after ac-

TABLE I

EFFECT OF CHANGE OF CARDIAC RATE ON DURATION OF SECOND SOUND—OPENING SNAP INTERVAL

CASE	INTERVAL BETWEEN BEGINNING OF SECOND SOUND AND OPENING SNAP, IN SECONDS	DURATION OF PRECEDING HEART CYCLE, IN SECONDS
Case 1	0.04	0.62
Rate accelerated by amyl nitrite.	0.06	0.67
	0.07	0.76
	0.07	0.79
Representative measurements during recovery stage.	0.08	0.80
	0.08	0.83
	0.08	0.85
	0.09	0.87
	0.09	0.90
	0.09	0.95
	0.09	0.97
Case 2	0.08	0.78
3/14/30	0.08	0.80
	0.09	0.88
5/31/30	0.10	0.92
	0.10	0.96
	0.10	0.96

*The basal diameter is a line drawn from the right cardiodiaphragmatic junction to the point on the left border between the left auricular appendage and the left ventricle.

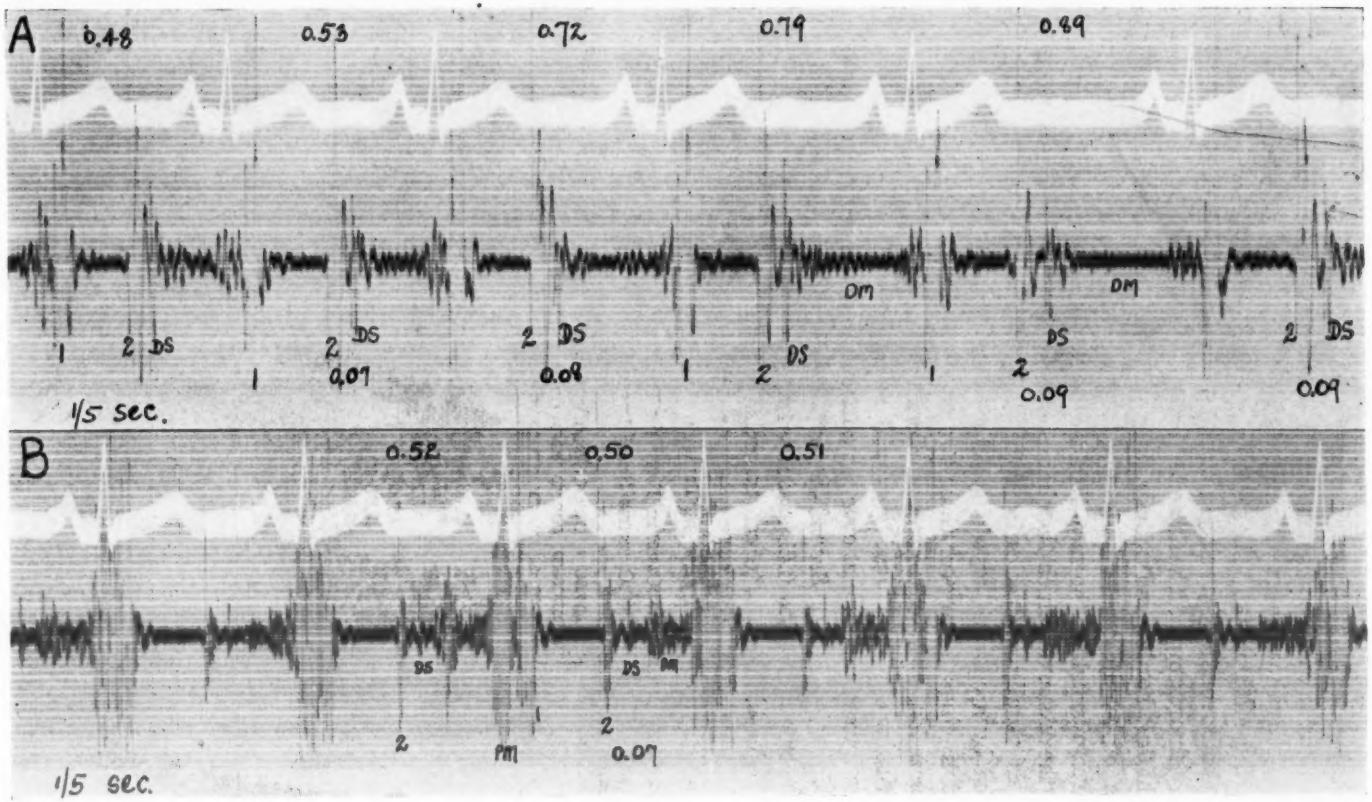

Fig. 2.—Upper tracing (*A*) recorded in third interspace shows a loud snap (DS) and insignificant diastolic and presystolic murmur (DM). The effect of sinus arrhythmia on the time relationship of the snap to the second sound is shown by comparison of the first two and the last two beats. The lower tracing (*B*) recorded in the fourth interspace shows the snap (DS) to be insignificant but the murmur prominent. The gaps between the second sound and the snap, and between the snap and the beginning of the typical murmur of well-developed mitral stenosis are clearly shown.

celerating the heart action by means of amyl nitrite). The longest was 0.19 second (after a very long preceding heart cycle in a case of auricular fibrillation with a widely split second sound). Short intervals are illustrated in Fig. 3 *A* and *B*, and long intervals in Figs. 4 and 7.

Cardiac rate appears to be a factor which affects the duration of the interval. This is evidenced by the fact that in a given individual if sound tracings are obtained showing substantial differences in cardiac rate, differences are found in the duration of the interval between the

TABLE II

DURATION OF SECOND SOUND—OPENING SNAP INTERVALS IN PATIENTS WITH SINUS RHYTHM

CASES	INTERVAL BETWEEN BEGINNING OF SECOND SOUND AND OPENING SNAP, IN SECONDS	DURATION OF PRECEDING HEART CYCLE, IN SECONDS
Case 1. C. D.	0.06	0.54
	0.06	0.53
	0.06	0.58
Case 2. C. S.	0.07	0.66
	0.07	0.61
Case 3. S. H.	0.06	0.76
	0.06	0.76
Case 4. S. S.	0.10	0.78
	0.10	0.78
	0.09	0.77
	0.10	0.76
Case 5. S. G.	0.10	0.83
	0.10	0.81
	0.10	0.83
Case 6. D. P.	0.09	0.95
	0.10	0.98
Case 7. R. M.	0.08	1.04
	0.07	0.95
	0.07	1.00
Case 8. J. W.	0.08	0.90
	0.08	0.96
	0.10	1.00
	0.10	1.08
Case 9. T. R.	0.06	0.93
	0.07	0.99
	0.06	1.00
	0.08	1.00
	0.07	1.03
	0.08	1.10
	0.08	1.14
	0.08	1.17
	0.08	1.22

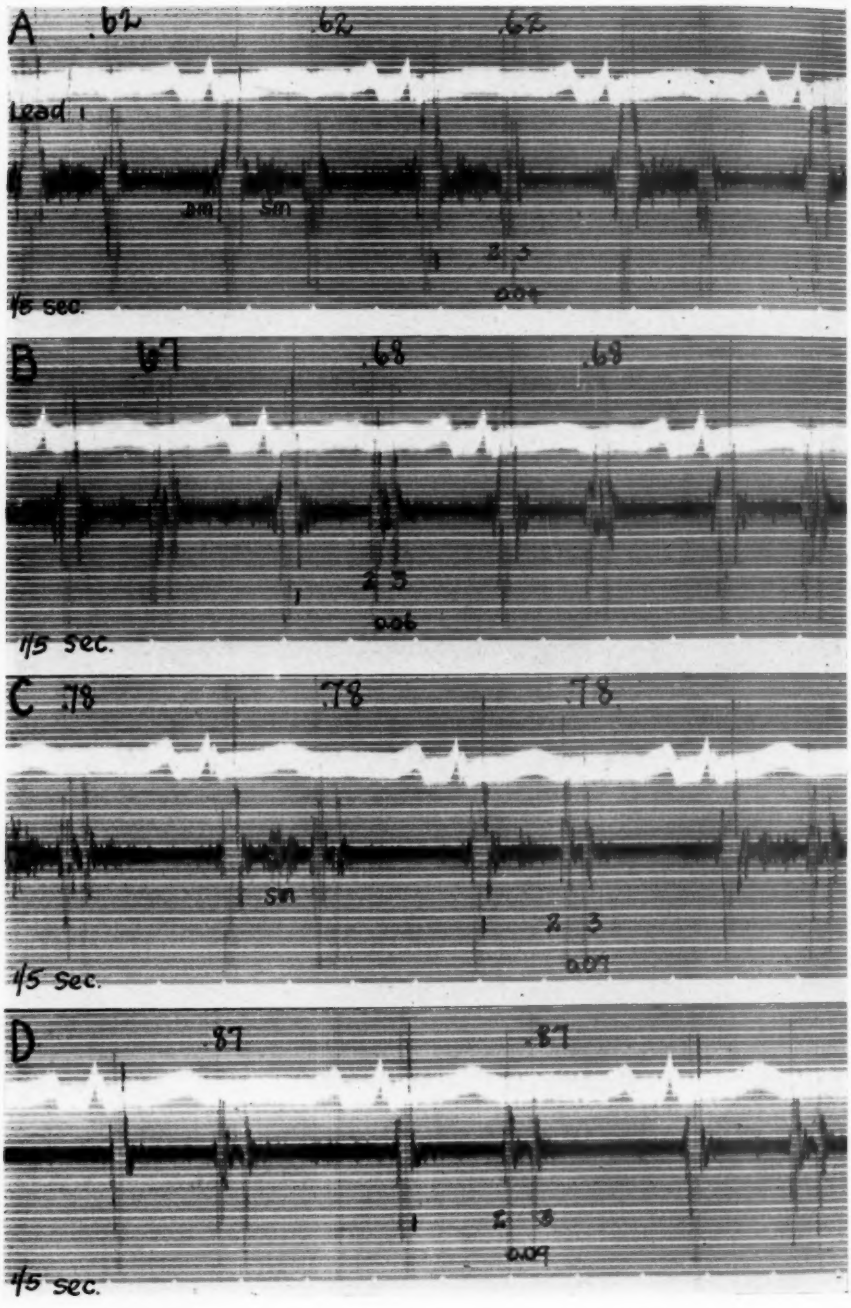

Fig. 3.—Mitral stenosis, opening snap. The effect of change of cardiac rate on the interval between the second sound and the opening snap. The heart cycle length of 0.62 second shown in *A* was produced by amyl nitrite, the cycle length of 0.68 second in *B* by excitement (being told she was to receive amyl nitrite), the cycle length of 0.78 second in *C* occurred during the recovery from amyl nitrite, and the cycle length of 0.87 second shown in *D* was recorded before the patient was told that she was to receive amyl nitrite. Tracings with time relationships similar to those of *D* were obtained after recovery from amyl nitrite. The interval between the second sound and the opening snap varied from 0.04 to 0.09 second becoming longer as the rate slowed.

beginning of the second sound and the snap. The changes tend to be in the same direction; as the length of the cardiac cycle increases, the duration of the interval increases (Table I and Fig. 3).

The above statements apply only to the variations observed in individuals. When the time relations in a series of cases were compared, no satisfactory correlation was observed between cardiac rate and the interval (Table II) except that all cases with rapid rate exhibited a short interval.

It is obvious, therefore, that other factors besides cardiac rate must be of importance in determining the time relationship of the snap to the second sound. The evaluation of such factors would be difficult. It is well known that the position of the second heart sound is determined by intraventricular and arterial pressure relationships. When intraventricular pressure falls below arterial pressure, the semilunar valves close and produce the second sound. As a rule the second sound occurs approximately at the end of the T-wave of the electrocardiogram, although it may come before or slightly after this event. If the snap is produced by the attempt of the stenosed mitral valve to open, as was suggested by Guttman, Sansom and Rouches, its time with respect to early ventricular diastole must be determined by the instant that left intraventricular pressure falls below left intra-auricular pressure. Thus since it is probable that the time incidence of both sounds depends on pressure relationships, in the one case of the ventricles and great vessels and in the other of the left auricle and left ventricle, it would seem that variation of the interval is possible under diverse circumstances.

The opening snap is heard in cases of auricular fibrillation quite as well as when the auricles are beating normally. In most cases of fibrillation there are changes in the time relation of the snap to the second sound from beat to beat which seem to depend on the duration of the preceding heart cycle (Fig. 4 and Table III). Variations of intervals are also found in association with other forms of irregularity of rhythm such as sinus arrhythmia (Fig. 2 *A* and Table II, Cases 8 and 9). After a short preceding heart cycle, the snap usually falls nearer the second sound. After a long period it usually falls later, and the interval separating it from the second sound is correspondingly greater.* These differences may be as great as 0.05 second. Very slight variations of the interval may also occur during regular rhythm, depending on the phase of respiration.

*Occasionally exceptions to this rule are found. In some cases beats falling early show a longer interval between the second sound and the snap. These exceptions apparently depend on early closure of the semilunar valves in relatively premature and feeble beats, leaving a larger share of the relaxation process than usual to be accomplished after semilunar closure. The relationship in comparatively premature beats between early semilunar valve closure and delay in the snap is shown in Fig. 5 and Table III (Case 7). It is also of interest that, in general, the intervals tend to be longer when auricular fibrillation is present than when the rhythm is normal. For this phenomenon, we have no explanation.

TABLE III

COMPARISON IN AURICULAR FIBRILLATION BETWEEN HEART CYCLE LENGTH AND DURATION OF SECOND SOUND—OPENING SNAP INTERVALS

CASE	INTERVAL BETWEEN BEGINNING OF SECOND SOUND AND OPENING SNAP, IN SECONDS	DURATION OF PRECEDING HEART CYCLE, IN SECONDS
Case 1. A. F.	0.08	0.51
	0.09	0.53
	0.10	0.76
	0.10	0.78
	0.11	0.89
	0.11	0.98
	0.12	1.32
Case 2. H. O.	0.07	0.54
	0.08	0.64
	0.09	0.72
	0.10	0.84
	0.11	0.96
	0.12	1.00
	0.12	1.08
	0.12	1.20
Case 3. C. H.	0.09	0.73
	0.10	0.79
	0.10	0.80
	0.11	0.82
	0.10	0.91
	0.11	0.92
	0.12	1.15
	0.11	1.39
	0.11	1.51
	0.12	1.61
Case 4. J. M.	0.10	0.78
	0.11	0.80
	0.11	0.81
	0.10	0.83
	0.11	1.00
	0.11	1.03
	0.11	1.12
	0.11	1.14
	0.11	1.16
	0.11	1.20
	0.11	1.26
Case 5. J. N.	0.06	0.55
	0.07	0.65
	0.08	0.70
	0.08	0.73
	0.09	0.74
	0.09	0.75
	0.08	0.76
	0.09	0.85
	0.09	0.92
	0.09	1.00
	0.10	1.15
	0.10	1.30
	0.11	1.45
	0.11	1.54

TABLE III—CONTINUED

CASE	INTERVAL BETWEEN BEGINNING OF SECOND SOUND AND OPENING SNAP, IN SECONDS	DURATION OF PRECEDING HEART CYCLE, IN SECONDS
Case 6. M. T.	0.07	0.48
	0.08	0.66
	0.08	0.71
	0.08	0.74
	0.09	0.77
	0.08	0.78
	0.09	0.82
	0.09	0.85
	0.09	0.93
	0.10	0.95
	0.09	1.31
	0.11	1.46
Slower rate	0.09	0.74
	0.09	1.02
	0.09	1.18
	0.10	1.31
	0.10	1.34
	0.10	1.35
	0.11	1.60
	0.10	1.69
	0.10	1.78
	0.10	1.80
Case 7. E. M.	0.10	0.49
	0.10	0.53
	0.11	0.54
	0.10	0.62
	0.09	0.75
	0.09	0.79
	0.10	0.86
	0.10	0.88
	0.11	1.16

Time Relation of Snap to Diastolic Murmur. According to both Guttman[3] and Rouches,[5] the snap marks the beginning of the diastolic murmur of mitral stenosis. Although this is the usual impression obtained by auscultation, sound records sometimes show the snap to precede the beginning of the murmur by an appreciable, though very short, interval (Fig. 2 *B*). This can occasionally be detected on auscultation.

The "*Auscultatory Gap.*" In cases of well-developed mitral stenosis which fail to show the snap, it is possible to record the auscultatory gap described by Lewis,[10] and Wilson and Wishart,[11] i.e., the interval between the second sound and the beginning of the murmur. This gap, which is clearly perceptible to the ear, has considerable value as a diagnostic sign of mitral stenosis. It is especially useful in differentiating a diastolic murmur arising at the mitral valve from one arising at either of the semilunar valves. The onset of the former is separated from the

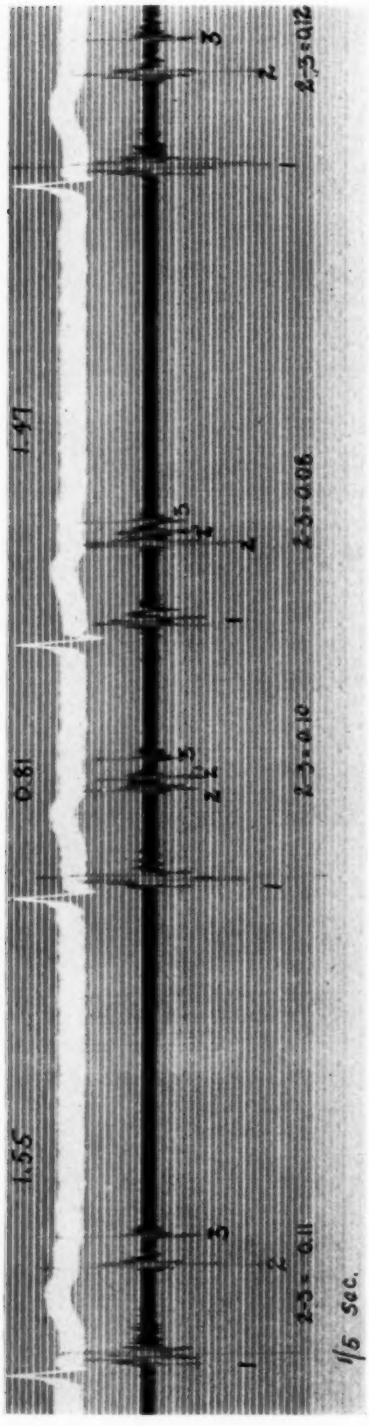

Fig. 4.—Mitral stenosis, auricular fibrillation, phasic reduplication of the second sound and opening snap. The second and third beats show reduplication of the second sound while the first and fourth fail to show reduplication. The snap is recorded in all. The presence or absence of reduplication in this case depended on the phase of respiration. In the third beat which falls after a shorter rest period, the interval between the second sound and the opening snap is shorter than in the other beats.

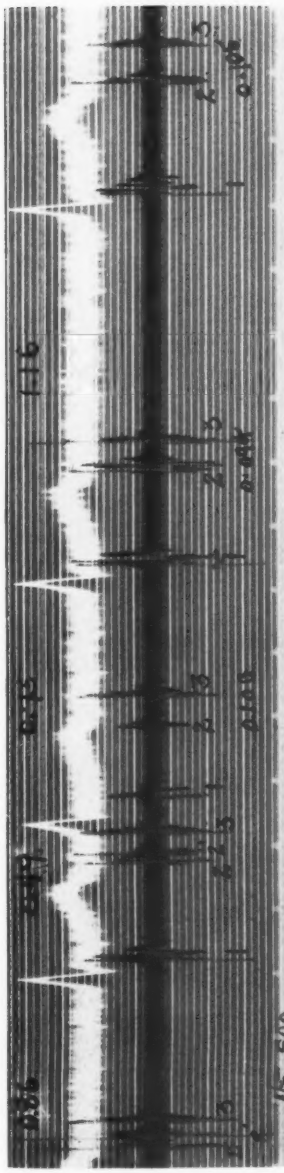

Fig. 5.—Mitral stenosis, auricular fibrillation, opening snap, phasic reduplication of the second sound. In the second beat, which is relatively premature, both the second sound and the snap fall earlier with respect to the end of the T-wave than in the less premature beats. The second sound has changed its position more than the snap, thus causing the interval between them to be greater than in less premature beats. This case consitutes the only exception we have encountered to the general rule that the interval varies in the same direction as the length of the preceding heart cycle.

second sound by this gap.* The murmur of either aortic or pulmonic regurgitation is continuous with the second sound, unless dynamic events on the two sides are asynchronous. Thus in one case with aortic regurgitation and bundle-branch block it was possible to detect on auscultation and to demonstrate by means of sound tracings a gap between the second sound and the aortic diastolic murmur.

Variation in the Sound Intensity of the Snap. The sound intensity of the snap may vary from time to time in a given individual, a fact first pointed out by Rouches.[5] In one of our patients, for example, the sound was not heard when she was sitting quietly (heart rate 70 beats per minute). After she had walked up and down the room several times it became distinctly audible, though not loud (heart rate 84 beats per minute). When the rate was still further increased (100 beats per minute), the snap became quite loud. It then decreased in intensity and finally disappeared as the heart rate declined. As a rule, the sound is more distinct when the patient is in the recumbent position. The reason for these differences is not known; possibly they depend on the level of intra-auricular pressure at the beginning of ventricular diastole, and the speed of ventricular relaxation.

Relation to Reduplicated Second Sounds. Rouches[5] was apparently the first to observe that the *claquement* and splitting of the second sound both may be present in the same heart cycle. Despite the fact that this is a common finding, readily confirmed by means of sound tracings, other writers do not mention it. When splitting of the second sound and the opening snap occur in the same heart cycle, it is of interest to note the time relations of the two components of the second sound to the opening snap. This can be studied under a variety of circumstances. Among cases with normal intraventricular conduction showing respiratory phasic splitting of the second sound, in which the doubling tends to occur during the inspiratory phase of the respiratory cycle, the snap maintained its time relationship with the first component of the split sound.†

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*Wilson and Wishart[11] state that the diastolic murmur of mitral stenosis is sometimes continuous with the second heart sound. We have never observed it. According to what is known of cardiodynamics, it would scarcely seem possible for a mitral diastolic murmur to be continuous with the aortic second sound. If, however, the second sound were widely split and pulmonic closure followed aortic closure, it is possible that the murmur might be continuous with the pulmonic component of the second sound. When reduplication of the second sound, the opening snap and a mitral diastolic murmur are all present, it should be possible to hear and record three short sounds followed by a murmur. The intervals between these sounds and the murmur are very short, so that registering apparatus without adequate damping records them as continuous vibrations resembling those obtained from murmurs. This point is illustrated in Fig. 9. In *A*, the three sounds recorded by means of the electrocardiographic string are not clearly separated and give the impression of a continuous sound. In *B*, in which damping is more adequate, the sounds are clearly separated.

†Katz[10] has found in experimental cardiodynamic studies that there is frequently appreciable asynchronism in the duration of ventricular systole on the two sides. Such asynchronism might be expected to cause splitting of either the first or the second heart sound or both. Our observations indicate that in cases of mitral stenosis with split second sounds and no electrocardiographic evidence of disturbed intraventricular conduction, aortic closure tends to precede pulmonic closure. It is, of course, entirely possible that the sequence might occasionally be reversed.

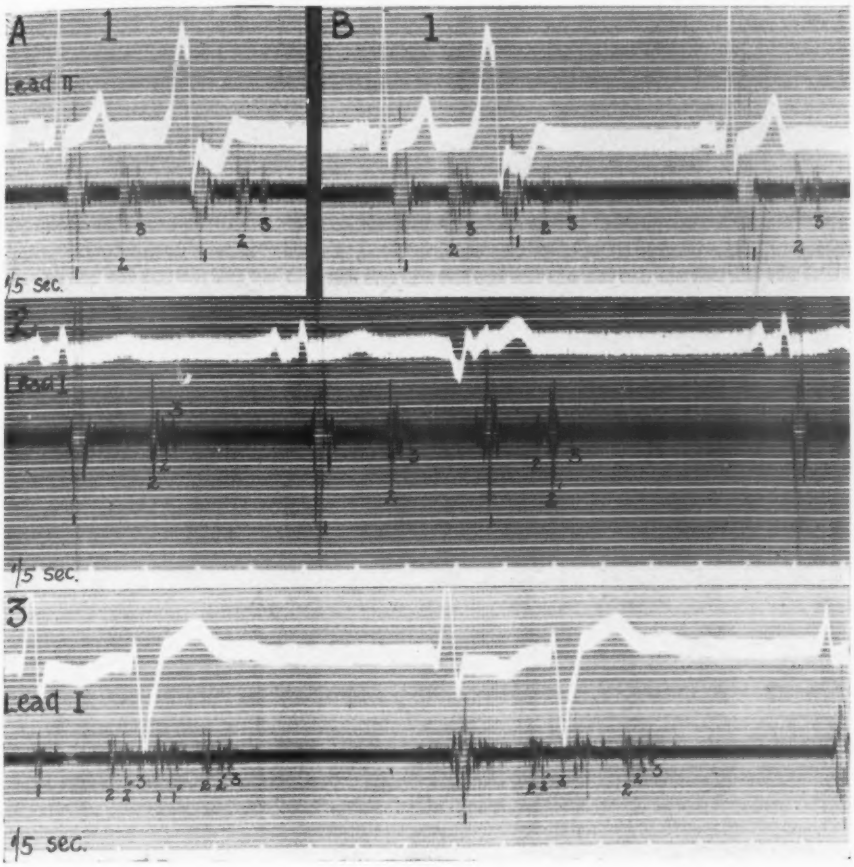

Fig. 6.—The time relations of the opening snap to the second sound in ventricular extrasystoles. In Strip 1-*A*, the extrasystolic second sound (2) is reduplicated, and the snap maintains its time relation with the second component. In Strip 1-*B*, the extrasystole is more premature, and the second component of the second sound drops out. The snap (3) cannot be related to the component of the second sound (2) recorded since the time interval is too great. Strip 2 was recorded from the same case as Strip 1 and is included to show the shape of the extrasystolic complexes in Lead I of the electrocardiogram. Strip 3 was obtained from another patient in whom, although the extrasystolic complexes differed materially from those of the first case, the main deflection was downward in Lead I. In this case the snap was invariably related to the first component of the split second sound.

The second sound is usually split both in ventricular extrasystolic beats and in the presence of bundle-branch defect.* Studies were made in two cases exhibiting the opening snap and numerous ventricular extrasystoles with split second sounds. The main QRS deflections of the extrasystolic beats, although differing considerably in shape in the two cases were downward in Lead I and upward in Lead III in both. In one case the snap invariably maintained its time relationship to the first com-

*Unpublished observations. It has long been known that the first sound may be split when bundle-branch block is present. King has recently ascribed diagnostic significance to this finding. The first sounds of ventricular extrasystoles also tend to be split.

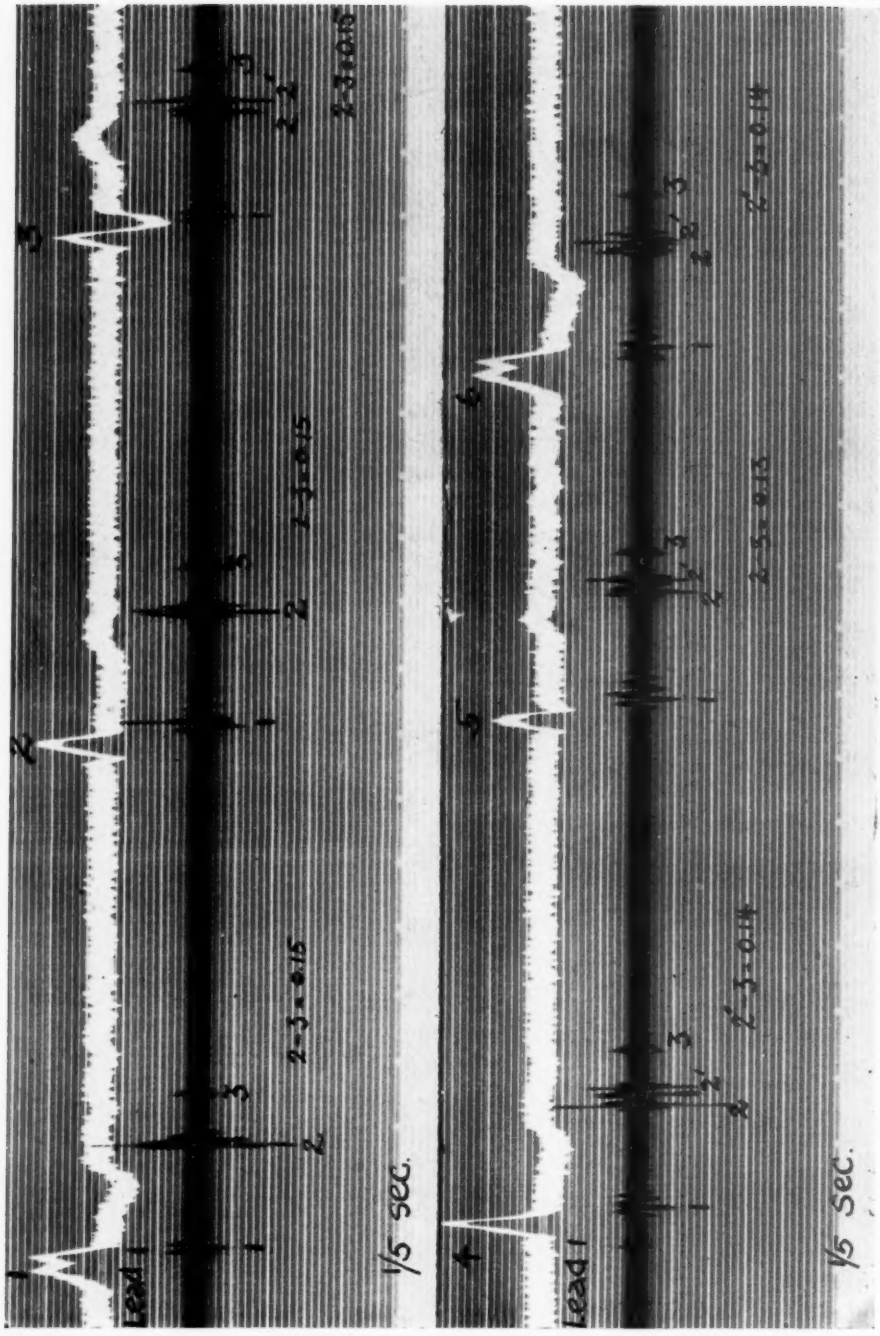

Fig. 7.—Mitral stenosis, auricular fibrillation, opening snap, various types of ventricular complexes. Four different types of beats (3, 4, 5 and 6) show splitting of the second sound (2, 2'). In beats 3 and 5, the snap (3) maintains its time relation to the first component of the split second sound and in beats 4 and 6 to the second component. In beat 1, the electrocardiogram is the same as in beat 6, yet no splitting is recorded. One component may be so faint as to fail to record on the two may be merged. This case exhibits the longest interval which we have observed between the second sound and the snap. In beats with short second sounds, the interval between one component of the second sound and the snap always fell within this range.

ponent and in the other case to the second component of the split second sound in the extrasystolic beats (Fig. 6). We have studied one case in which a variety of aberrant ventricular complexes was recorded (Fig. 7). Four different types exhibited splitting of the second sound. In two types, the snap maintained a constant relation to the first component of the second sound and in the other two types to the second component. One of these types of beats fulfilled the electrocardiographic criteria of bundle-branch block (Fig. 7, beats 1 and 6). According to the views of Wilson and his associates,[17] the block was left-sided since the main QRS deflection was upward in Lead I and downward in Lead III. In all beats of this type in which splitting of the second sound was recorded, the snap invariably maintained a significant time relationship to the second component of the split sound.*

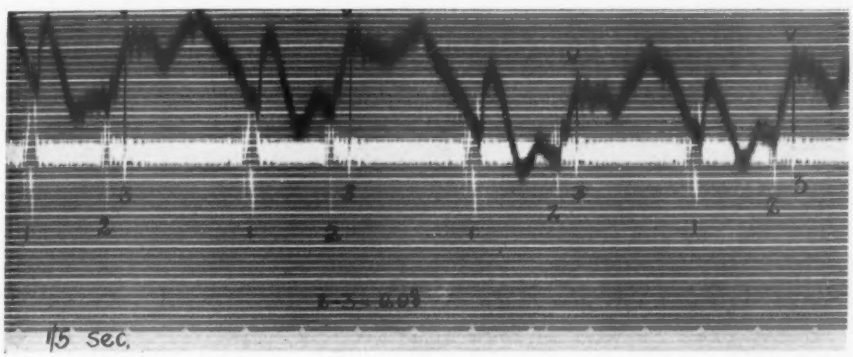

Fig. 8.—Mitral stenosis and opening snap. Sound tracing (recorded with electrocardiographic string) and optically recorded jugular phlebogram. The snap (3) and the summit of the V-wave are practically simultaneous.

Relation to Jugular Pulse. The comparison of the time relations of the opening snap and the jugular pulse, recorded without parallax, was made in eight cases. These tracings show that the opening snap occurs approximately synchronously with the summit of the V-wave (Fig. 8), provided the second sound is not reduplicated.

The summit of the V-wave is supposed to mark the end of the isometric relaxation phase and the beginning of right ventricular filling. This relationship held as constantly in the cases with auricular fibrillation as in those with normal rhythm, despite the fact that in the former the time interval between the beginning of the second sound and the snap varied from beat to beat. When this occurred the interval between the second

*The time relationships of the snap to split second sounds in ventricular extrasystoles and bundle-branch block have a bearing on the question as to the spread of the excitatory process in these conditions. This will be considered in connection with other evidence in a subsequent publication. It might be said, however, that the evidence presented here supports the views of Wilson and his associates with respect to the side of origin of bundle-branch block and those ventricular extrasystoles which have electrocardiographic complexes similar to those of bundle-branch block. It is questionable, however, as to whether a sharp dividing line between right and left ventricular extrasystoles can be established on the basis of the direction of the main deflections in Leads I and III.

sound and the V-wave showed the same variation. In two cases studied by this method, a phasic respiratory incidence of splitting of the second sound was present. In both these cases, when the second sound was single, the time of the snap and the summit of the V-wave coincided. This result was the same as that obtained in the other six cases. When

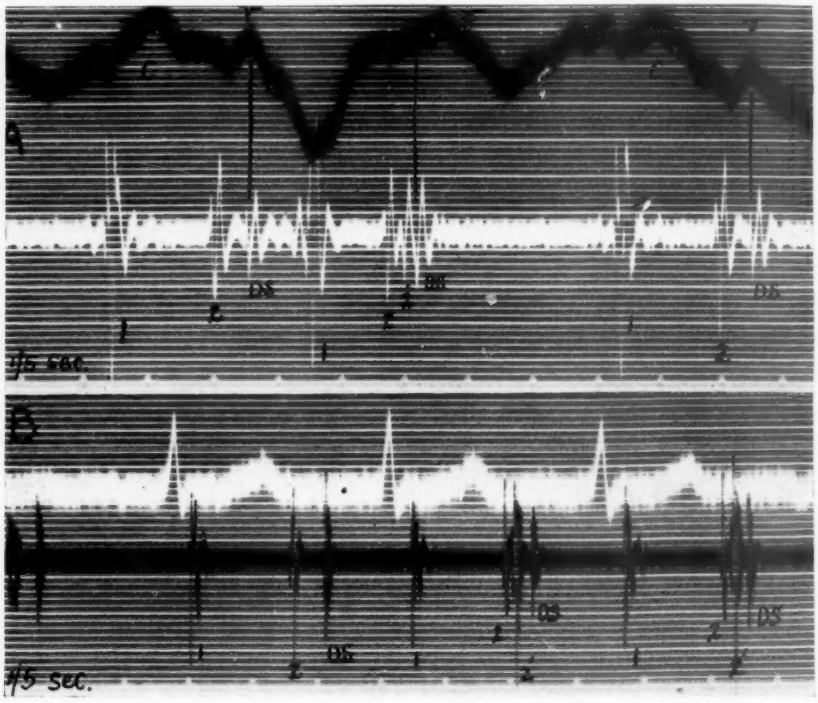

Fig. 9.—Mitral stenosis, auricular fibrillation, phasic (respiratory) reduplication of the second sound, opening snap. In *A*, the time relations of the jugular pulse and sounds recorded by means of the electrocardiographic string are compared. In the first and third beats, in which the second sound is single, the snap falls at the summit of the V-wave. In the second beat, there is reduplication of the second sound. (Due to the poor sensitivity and damping qualities of the string, the two elements of the reduplicated second sound and the opening snap resemble a murmur.) Note how far the summit of the V-wave in this beat lags behind the snap. The time interval between the second component of the second sound and the V-wave is practically identical with the interval between the single second sounds of the first and third beats and the summit of the respective V-waves. This indicates that the second component of the split second sound is due to pulmonic closure. The sound tracing in *B* was recorded from the same position (fourth left interspace) by means of a very small rubber cement membrane sensitive to waves of high frequency and with excellent damping. When reduplication of the second sound is present, the three sounds in rapid succession are clearly recorded.

the second sound was split, however, pulmonic closure lagging after aortic, the snap tended to precede the summit of the V-wave (Fig. 9).

It would appear, therefore, that reduplication of the second sound tends to be accompanied by a similar degree of asynchronism between the summit of the V-wave, which is a right-sided phenomenon, and the opening snap, which is left-sided in origin.

Relation to Excursion of Left Ventricular Border. The relation of the snap to excursion of the left ventricular border was studied in six cases. Simultaneous electrocardiograms and roentgen kymograms* of the left ventricle were made. Simultaneous electrocardiograms and sound tracings were also taken in the same individuals, with care to avoid

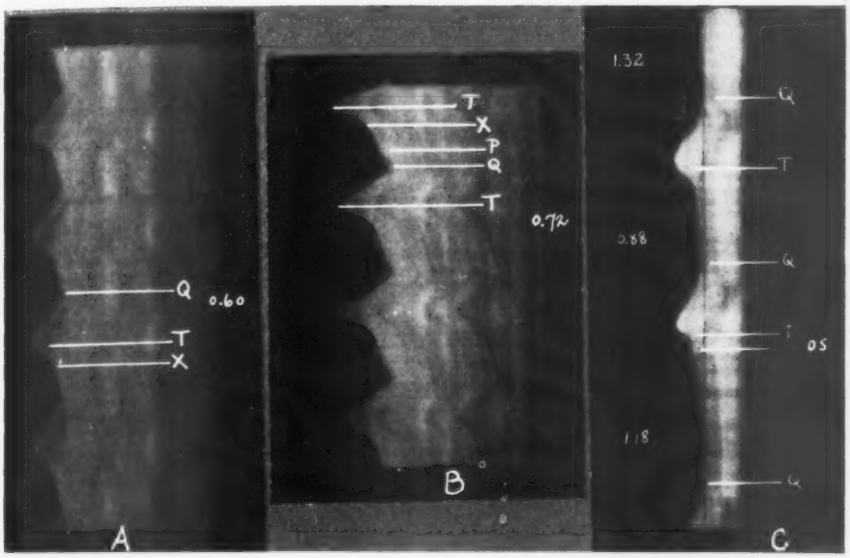

Fig. 10.—Roentgen kymograms of the left ventricle in three cases of mitral stenosis with opening snap. The dark shadow is produced by the heart. The tracing should be read from above downward. The letter *P* identifies the position of the beginning of the P-wave of the electrocardiogram, *Q* the beginning of the QRS complex, and *T* the end of the T-wave in Lead I. The position of the opening snap (X) as calculated for *A* and *B* falls just at the point of angulation which apparently marks the end of the period of passive rotation. The gradual outward movement following this point must be due to ventricular filling. In *C*, a case of auricular fibrillation, the opening snap (DS) does not come at the point of angulation in the curve but follows it. Note that the slow outward movement of the ventricle does not begin until after the time of the snap. The position of the snap was calculated from measurements of its time relations to the T-wave of the electrocardiogram in beats with approximately the same preceding heart cycle length. In such beats the variation in the time interval between the end of the T-wave and the beginning of the snap does not tend to exceed 0.01 second.

parallax. By a comparison of these two records it was possible, if the rate remained fairly constant, to identify fairly accurately the point on the roentgen kymogram at which the opening snap occurred and thereby to relate it to a certain point in the excursion of the left ventricular border.

It will be seen in Fig. 10 that there is a point of angulation in the early diastolic part of the left ventricular curve. The sharp outward thrust

*The roentgen kymograms were made by placing a horizontal slit 1.5 mm. wide over the part of the cardiac border whose movement was to be recorded. The film was moved past this point in a motor driven casette holder at a constant rate and a continuous roentgen ray photographic record made. By this method the horizontal movement of the border may be recorded. Cardiac roentgen kymography was introduced by Gött and Rosenthal.[15] Simultaneous electrocardiograms and roentgen kymograms were published recently by Stenström and Westermark,[19] but these authors reproduce only drawings of their results.

of the left ventricle which just precedes this point, begins too early to be caused by diastolic filling. It is due to rotation of the heart in the process of relaxation, after having been actively rotated in the opposite direction during systole. Following this point of sharp angulation the outward movement of the heart border is much more gradual. This gradual outward movement is due to ventricular filling. The position of the opening snap was approximately at this point of angulation in the roentgen kymograms in four of the six cases studied by this method (Fig. 10 *A* and *B*). In one case, however, the snap occurred before the movement of rotation was completed, and in another case it did not occur until an appreciable interval after rotation was completed and the ven-

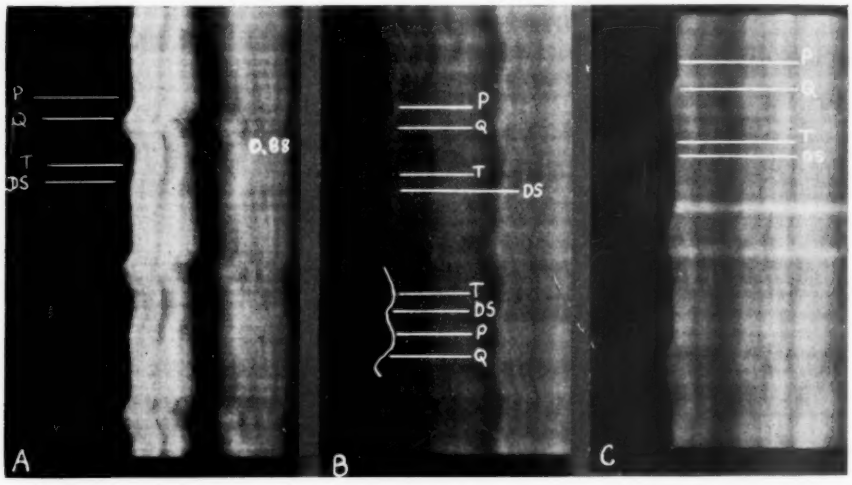

Fig. 11.—Roentgen kymograms of left auricular movement in three cases of mitral stenosis. The point *P* identifies the beginning of the P-wave of the electrocardiogram made simultaneously with the kymogram; *Q* identifies the beginning of the QRS complex, and *T* the end of the T-wave in Lead I. *DS* indicates the position of the opening snap (calculated from combined sound tracing and electrocardiogram). The chief excursion of the auricular wall in all three cases follows auricular contraction. In *A* and *B*, a distinct niche is observed at the instant of the opening snap. In *C*, the left auricle was very large and the excursion small. In this case, only a small niche appeared at the time of the snap.

tricular wall was practically motionless (Fig. 10 *C*). Thus while it may be said that the snap falls at about the time of the completion of passive rotation of the ventricles, it does not bear an exact time relationship to the process of rotation, since it may either precede or follow the end of rotation.

Relation to Excursion of Left Auricular Border. Roentgen kymograms of the left auricle were also attempted in a number of cases exhibiting a well-defined opening snap, and in normal controls. This procedure presents certain technical difficulties which need not be discussed here. The most satisfactory proof that the curve is due, at least in part, to auricular movement is the presence of a wave of contraction corresponding to the P-wave of the electrocardiogram. Satisfactory

curves have thus far been obtained in seven cases of mitral stenosis,* in two normal controls and in two controls with mitral regurgitation.

It was thought that if the snap is due to sudden curtailment of the opening movement of the stenotic mitral valve, one should find in the movement of the left auricular wall a slight inward thrust just preceding the snap (due to the opening movement of the valve) and possibly also an outward thrust just after the snap (due to a reflected wave produced by sudden curtailment of valve movement). In five of the seven cases this prediction was fulfilled completely (Fig. 11). In the other two cases, however, no well-defined movement of the auricular wall in early

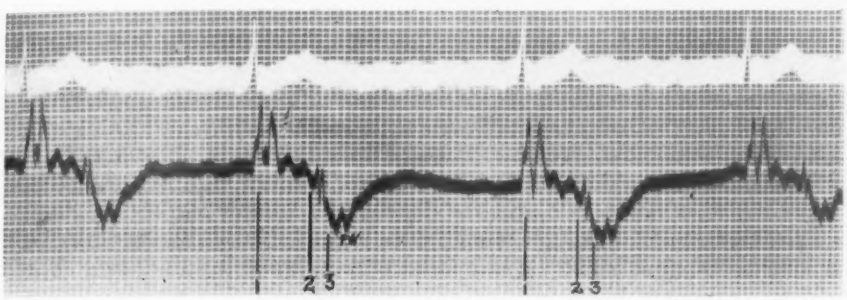

Fig. 12.—Mitral stenosis, opening snap, auricular fibrillation. Electrocardiogram and optically recorded apex cardiogram. The position of the snap on the apex cardiogram is calculated from similar cycles on a sound tracing recorded with the electrocardiogram. The snap precedes the beginning of the protodiastolic wave (PW) of the apex cardiogram, by approximately 0.04 second. This wave is usually insignificant when mitral stenosis is present.

diastole could be detected on the films. Possibly the failure in these two cases was due to marked dilatation of the left auricle and to high degree of stenosis, both of which would tend to minimize excursion of the auricular border. In none of the normal controls was the slight inwardly projecting niche seen.

Relation to Apex Cardiograms. Optically recorded apex cardiograms in mitral stenosis usually show either an insignificant protodiastolic wave or none at all. When apex cardiograms and the sounds are recorded without parallax, the opening snap usually precedes the beginning of the protodiastolic wave if one is present, by approximately 0.02 to 0.04 second (Fig. 12). This is in contrast to the relationship in protodiastolic gallop rhythm and the physiological third heart sound in which the peak of the wave and the gallop sound are practically synchronous (observations to be published).

MECHANISM OF PRODUCTION

The hypothesis that the opening snap is due to limitation of the opening movement of a stenosed mitral valve was supported by Guttman,[3] Sansom,[4] Rouches[5] and others substantially on the following evi-

*This work is being carried further in the attempt to study the effect of mitral stenosis on the movements of the auricular wall.

dence: (1) The sound apparently occurs only in the presence of mitral stenosis. (2) It is heard best over the body of the heart or at the apex. (3) It is a short sharp sound such as might be expected from a valvular rather than a muscular event. (4) It apparently marks the beginning of the diastolic murmur. (5) It is not part of a reduplicated basal second sound.

Our observations indicate that the above statements require two modifications. The snap does not clearly mark the beginning of the diastolic murmur but tends to precede it by a short, although appreciable, interval. The point of maximum loudness of the snap is not at the apex, as was taught by both Guttman and Sansom and accepted since their time, but is slightly above and to the right of the position at which the murmur is best heard. These modifications do not weaken, but on the contrary rather strengthen the contention that the snap is produced by the opening of the stenosed mitral valve. Nevertheless such evidence can scarcely be regarded as conclusive, and it therefore seemed advisable to subject the hypothesis to further test for which the data described above were accumulated.

The following statements may be made regarding the mechanism of production of the sound:

1. Auricular beating is not concerned in the production of the snap. The sound is frequently present during auricular fibrillation. Moreover, when the auricles are beating coordinately, the snap occurs independently of auricular beats.

2. The snap is not due to reduplication of the second sound. It can be demonstrated by means of sound tracings that if the second sound becomes reduplicated, the snap tends to maintain its characteristic time relationship with one of the two components of the reduplicated sound. As has been pointed out above, there are certain circumstances under which the relationship is maintained with the first component and other circumstances under which it is maintained with the second component. Thus reduplication of the second sound and the opening snap should not be confused with each other.

3. Ventricular filling cannot be responsible for the production of the snap. In cases of fairly well-advanced mitral stenosis, the beginning of the murmur as registered in sound tracings tends to be marked by relatively large vibrations. The snap may precede these vibrations by as much as 0.04 second. Thus the snap comes before blood flow of significant amount from auricles to ventricles. Furthermore the nature of the valvular lesion tends to prevent precipitous ventricular filling. This is indicated by the fact that protodiastolic waves of the apex cardiogram are usually either insignificant or absent in mitral stenosis. These waves are practically synchronous with the beginning of the diastolic murmur. Moreover, if the snap were the result of ventricular filling, it should be

present in normal cases with mitral valves capable of opening widely, with no hindrance to ventricular filling.

4. Neither relaxation of the ventricles nor passive rotation to a resting position is responsible for the snap. The loudness and sharpness of the sound, as well as the position over which it is best heard, render such an explanation of its mechanism improbable. Furthermore, if this were the cause of the sound, it should be present in other hearts whose ventricles pulsate vigorously, such as are found in the presence of hyperthyroidism. The roentgen kymograms, however, show that, in some cases, the snap may occur either before or after passive rotation has been completed. This mechanism may, therefore, be excluded as a factor in the production of the sound.

5. The above-mentioned cardiodynamic factors having been excluded as responsible for the production of the snap, the problem apparently narrows itself to a consideration of the opening movement of the stenosed mitral valve. First of all, it is necessary to determine, as nearly as possible, whether this event occurs at the same instant as the snap. There are at least two methods by which evidence may be obtained on this point: (a) comparison of time relation of the snap to the descending limb of the jugular V-wave and (b) comparison with the movements of the left auricular border.

(a) According to Wiggers[20] the end of the isometric relaxation phase is marked by a drop in the venous pulse. This drop in venous pulse must be due to opening of the tricuspid valve permitting blood flow from the right auricle and veins into the right ventricle. If these events occur synchronously on the two sides of the heart, the beginning of the fall of venous pressure in the jugular phlebogram (descent of the V-wave) should mark the opening of the mitral valve as well as the tricuspid. Factors that influence one should have an equal effect on the other. If, therefore, the snap is due to sudden limitation of the opening movement of the mitral valve, it should occur at practically the same instant as the beginning of the descent of the V-wave, unless asynchronism of dynamic events in the two ventricular chambers is present.

The results of our studies in eight cases clearly demonstrate these time relations between the beginning of the descent of the V-wave and the snap. It is equally significant that these two events are practically simultaneous when the second sound is single (and dynamic phenomena on the two sides of the heart practically synchronous) and that they are not simultaneous when the second sound is split. These facts indicate that the snap is related to opening of the mitral (but not the tricuspid) valve.

(b) The results obtained by left auricular roentgen kymography have a bearing on the mechanism of the snap. The presence in five out of seven cases of a distinct inward thrust in the curve of left auricular

movement, which ends at the instant the snap occurs and is followed by a short outward movement indicates that the process of auricular emptying is temporarily interrupted at the very beginning of the process. In the two cases that this phenomenon could not be recognized the left auricles were very large, so that little movement of the wall occurred at any time. In the two normal cases and also in the two cases of mitral regurgitation without stenosis, in all of which the excursions of the left auricle were fairly wide, this peculiar niche in the curve was absent. It is clear from these data that the snap occurs as the auricle makes its first attempt to empty and that in cases in which the snap is present, there tends to be a temporary interruption of the emptying process immediately after the snap. The outward movement of the auricular wall following the inward movement could be caused by (1) a reflected wave from the mitral valve whose opening movement was suddenly curtailed; (2) inflow of blood from the pulmonary veins, auricular emptying having been temporarily retarded; or (3) a combination of these two factors. In any event the snap is identified in time with the sudden curtailment in the opening movement of the mitral valve.

Thus all the evidence we have been able to collect is consistent with the hypothesis that the snap is due to sudden curtailment of the opening movement of the mitral valve.

At this point the hypothesis proposed by Gallavardin,[9] that the sound is due to a "shock-like" wave transmitted from the aortic to the mitral valve must be considered, particularly since it has been supported recently by Mozer and Duchosal.[13] Two objections to this hypothesis should suffice: (1) Even if it were conceivable that a wave could travel so slowly from the aortic to the mitral valve as to produce a sound after 0.06 to 0.15 second, it would not be possible for such a slowly advancing wave to be responsible for the production of a sharp sound. (2) The fact that the summit of the V-wave and the snap occur simultaneously (when the second sound is single) even in cases of arrhythmia in which the time intervals after the second sound may vary considerably from beat to beat, eliminates Gallavardin's hypothesis. The hypothetical "shock-like" wave could not be expected to vary its speed from the aortic to the mitral valve in correspondence with variation in the interval between the second sound and the summit of the V-wave, since the time of the latter is determined by the beginning of right ventricular filling, whereas the former would have to depend on aortic closure.

In justice to Gallavardin, it should be stated that at the time his hypothesis was proposed, he assumed that the mitral valve opened immediately after aortic closure. The development of physiological knowledge regarding the time intervals between semilunar valve closure and A-V valve opening (the so-called isometric relaxation phase) has made his hypothesis untenable.

The evidence in favor of the view that the snap is produced by sudden limitation of the opening movement of the stenosed mitral valve may be summarized as follows: (1) The sound apparently occurs only in the presence of mitral stenosis. (2) It is the type of sound which might be expected from sudden vibration of a valve. (3) The position at which it is best heard favors its production either at the mitral valve or in its vicinity. (4) It is entirely independent of auricular contraction. (5) It precedes both the diastolic murmur and effective ventricular filling. (6) It may be synchronous with, precede or follow the completion of passive rotation of the ventricles. (7) It comes, as is shown by combined sound tracings and jugular phlebograms and by auricular roentgen kymograms, at the instant when opening of the mitral valve is to be expected. (8) So far as is known, no other cardiac event capable of producing a sound is occurring at this instant.

DIFFERENTIAL DIAGNOSIS

The chief reason why the opening snap has failed to win for itself prominence as a diagnostic sign of mitral stenosis is due to the fact that it has never been clearly enough differentiated from certain other sounds. The confusion which exists is exemplified in a recent contribution by a distinguished investigator of rheumatic heart disease,[21] who writes that one of the signs of mitral stenosis is a doubling of the second sound at the apex. The writer apparently appreciates the diagnostic significance of this physical sign. The term is unfortunate, since, as has been pointed out above, (1) doubling of the second sound is not characteristic of mitral stenosis and (2) neither doubling of the second sound nor the opening snap is heard best at the apex.

The sounds which must be considered in the differential diagnosis of the opening snap are: (a) reduplication of the second sound; (b) protodiastolic gallop sounds; (c) the physiological third heart sound; and (d) midsystolic clicking sounds. The important differential points include: (1) character of the sounds; (2) areas over which they are best heard; and (3) time relations.*

The character of the sounds and the area of maximum audibility are best determined by auscultation and the time relations by sound registration. It is possible, however, to train the ear to detect remarkably small differences in short intervals. In our experience the trained observer learns to estimate from auscultation the duration of intervals up to 0.12 second with an accuracy of approximately ± 0.02 second.

(a) Reduplicated second sounds are heard best either at the level of the second or third, rarely the fourth interspace, over the sternum or just to the left of it. The sounds are always louder at the base than in

*We have recently constructed a table in which certain important characteristics of the various "extra" heart sounds of value in the differential diagnosis are given.[22]

the area over which the opening snap is heard best. Localization is usually more readily made in the case of high-pitched, sharp sounds whose character resembles that of the snap. The time interval between the two sounds is usually shorter than in the case of the snap but occasionally does exceed 0.06 second. Under such circumstances, the time relation loses its value as a differential point. There is frequently marked phasic respiratory variation in the intervals between split second sounds. Phasic variation between the second sound and the snap in the absence of arrhythmia is so slight as to be inappreciable on clinical examination.

(b) The protodiastolic gallop and (c) physiological third heart sounds are so similar in their characteristics that they may be considered together in the differentiation from the snap. They are heard best, as a rule, in the neighborhood of the apex.* They are low-pitched, dull sounds, thus differing strikingly in character from the opening snap. These sounds occur in a range of approximately 0.12 to 0.20 second after the second sound, the length of the interval depending to some extent on the cardiac rate.† If the influence of cardiac rate on the interval is taken into consideration, there are comparatively few cases in which this time relation loses its value as a differential point.

(d) Clicking or snapping sounds sometimes occur during ventricular systole,[22] coming between the first and second sounds. These sounds frequently resemble the opening snap and sometimes have a similar area of maximum audibility. They will not be confused, however, if the examiner orients himself as to which is the first and which the second sound.

CLINICAL IMPORTANCE OF THE OPENING SNAP

The opening snap may be regarded as having a value for the diagnosis of mitral stenosis scarcely second to that of the characteristic diastolic murmur. In this respect it has two great advantages: (1) It is easily differentiated from all other sounds, and (2) it is clearly audible in many cases in which the murmur is so insignificant as to be easily missed. It may, therefore, save the examiner the embarrassment of failing to hear a significant murmur. Furthermore, it is present in some cases in which the murmur cannot be elicited. In every case of this type which we have observed, there were other signs pointing to the diagnosis of mitral stenosis.

According to Rouches, the sound is absent either in very early or in advanced mitral stenosis, in the former because the valves are not bound down enough to snap and in the latter because they have lost their mobility. We have not been able to make sufficient necropsy examina-

*There is one exception to this statement. Right-sided gallop rhythm is usually heard best in the neighborhood of the lower part of the sternum.
†Unpublished observation.

tions of material studied clinically to confirm or to disprove Rouches' view. In five cases, however, in which we failed to elicit the opening snap, the valves were found to be greatly thickened and practically immobile. Another point which might be regarded as in favor of Rouches' hypothesis is the fact that the snap is less frequently heard in young children with mitral stenosis, than in adults. Whether this is because valve crippling is usually less advanced in children is not known.

The evidence, therefore, appears to indicate that the presence of the opening snap may be regarded as practically pathognomonic of mitral stenosis. Its absence, however, is not to be construed as a point against the diagnosis.

SUMMARY

1. The opening snap (*claquement d'ouverture de la mitrale*) can be heard and recorded in more than half the cases of mitral stenosis. It has not been observed in the absence of mitral stenosis. It is one of the most important diagnostic signs of this valvular lesion.

2. The chief characteristics of the opening snap are the following: (a) The sound is a sharp snap or click. (b) It has been found to occur from 0.03 to 0.19 second after the beginning of the second sound, the ordinary range being 0.06 to 0.11 second. (c) It is usually loudest in the fourth left interspace, occasionally in the third, slightly above and to the right of the area in which the diastolic murmur is best heard. (d) It precedes the onset of the murmur by a short interval. (e) It is usually best elicited with the patient in the recumbent position. (f) In some cases it can be brought out by exercise and by increase of the cardiac rate. (g) It tends to be louder when the rate is rapid.

3. The interval between the second heart sound and the opening snap is influenced by the cardiac rate, tending to become shorter as the rate increases. Variations in the duration of this interval occur during auricular fibrillation and sinus arrhythmia depending on the length of the preceding heart cycle.

4. The opening snap is easily differentiated from reduplication of the second sound, protodiastolic gallop sounds, the physiological third heart sound and systolic clicking sounds.

5. The time relations of the opening snap, as observed from comparisons of sound tracings with electrocardiograms, apex cardiograms, jugular phlebograms, auricular and ventricular roentgen kymograms, exclude auricular contraction, ventricular rotation or filling, or shock-like waves transmitted from the aortic to the mitral valve, as factors in its production. All the evidence thus far available is in accord with the hypothesis that the sound is produced by the sudden limitation of the opening movement of a stenosed mitral valve which occurs in early diastole as soon as the left ventricle relaxes sufficiently to permit the pressure of the auricular blood column to become effective.

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THE FORM OF PREMATURE BEATS RESULTING FROM DIRECT STIMULATION OF THE HUMAN VENTRICLES*

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In 1930, Barker, Macleod and Alexander[1] reported the first observations upon the form of electrocardiographic curves derived from artificial stimulation of known areas upon the exposed human ventricles. A large number of points upon the epicardial surface of both ventricles were stimulated electrically, and the resulting deflections were recorded simultaneously in the three customary leads of the electrocardiogram. The curves were such as to lead these authors to conclude:

"(a) Ventricular premature contractions of right ventricular origin are represented in the electrocardiogram by ventricular complexes in which the chief initial deflection is upward in Lead I. Ventricular premature contractions of left ventricular origin are represented in the electrocardiogram by ventricular complexes in which the chief initial deflection is downward in Lead I.

"(b) The clinical electrocardiograms at present ascribed to block in the right branch of the His bundle indicate block in the left branch, and vice versa.

"(c) In so-called left ventricular preponderance the electrocardiogram is dominated by right ventricular effects and vice versa."

The conclusions drawn from their observations are of such importance to physiology, and the subsequent work to which they have led is so far-reaching in its implications that it has seemed desirable they should not rest upon a single case. Clearly, the opportunities for similar observations do not often present themselves, but we have recently been able to repeat the crucial part of their observation by inducing premature beats under direct observation from the two ventricles. It has seemed of some importance to place these upon record as confirmation of the valuable contribution of Barker and his collaborators, because observations upon a single patient, however precise and extensive they may be, are always subject to the criticism that the patient might have been exceptional in some important respect.

The patient, a man of thirty-eight years, entered the hospital on May 27. He had suddenly developed, eight days previously, pain in the left side of the anterior chest, fever, cough and sputum. He became steadily worse, and was gravely ill at the time of his admission to the hospital. The temperature was 103°, the pulse rate 130 and the respirations 30 per minute. Physical examination revealed clear signs of fluid in the right pleural cavity, with considerable displacement of the heart

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to the left. There was also a widespread pericardial friction rub. A needle was inserted into the pleural cavity through the fourth right intercostal space anteriorly, and a considerable quantity of greenish-yellow pus withdrawn. A direct smear from this material showed lancet-shaped diplococci, and cultures yielded Type 3 pneumococci.

The patient was immediately transferred to the Surgical Service and thoracostomy was performed, a portion of two ribs being removed in the right anterior axillary line, and suction drainage started. Despite fairly satisfactory drainage of the empyema cavity, the patient's general condition did not improve. On June 6, exploratory puncture of the peri-

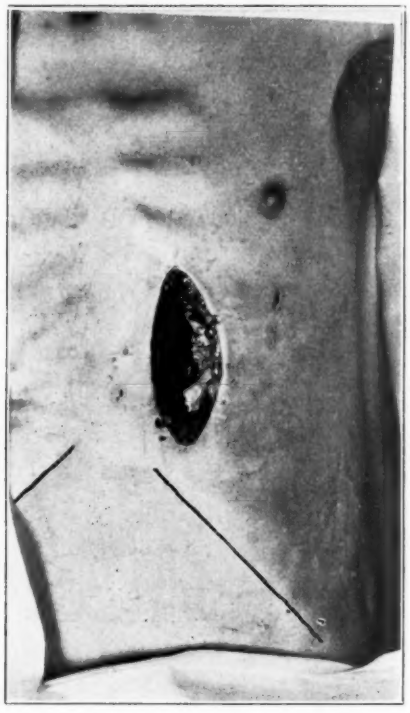

Fig. 1.—Photograph of thorax showing location of the opening through which the ventricles were stimulated. The approximate line of the costal margin is indicated by ink lines.

cardium revealed pus, and pericardiotomy was performed at once, with the removal of about 600 c.c. For the next few days he seemed slightly better, although the purulent discharge from the pericardium did not decrease, but after June 15 he grew steadily worse and died on June 19.

It is of some importance to state that this man had been in the hospital two years previously because of acute lobar pneumonia. Physical examination and roentgenograms at that time revealed no evidence of heart disease. He had never suffered from dyspnea on ordinary exertion, from orthopnea, or edema of the lower extremities, and stated that he

had never had rheumatic fever, chorea, tonsilitis, scarlet fever or diphtheria. It seems highly probable, therefore, that his heart was normal at the beginning of the acute illness from which he died. Careful postmortem examination of the heart failed to disclose evidence of disease of the myocardium or valves.

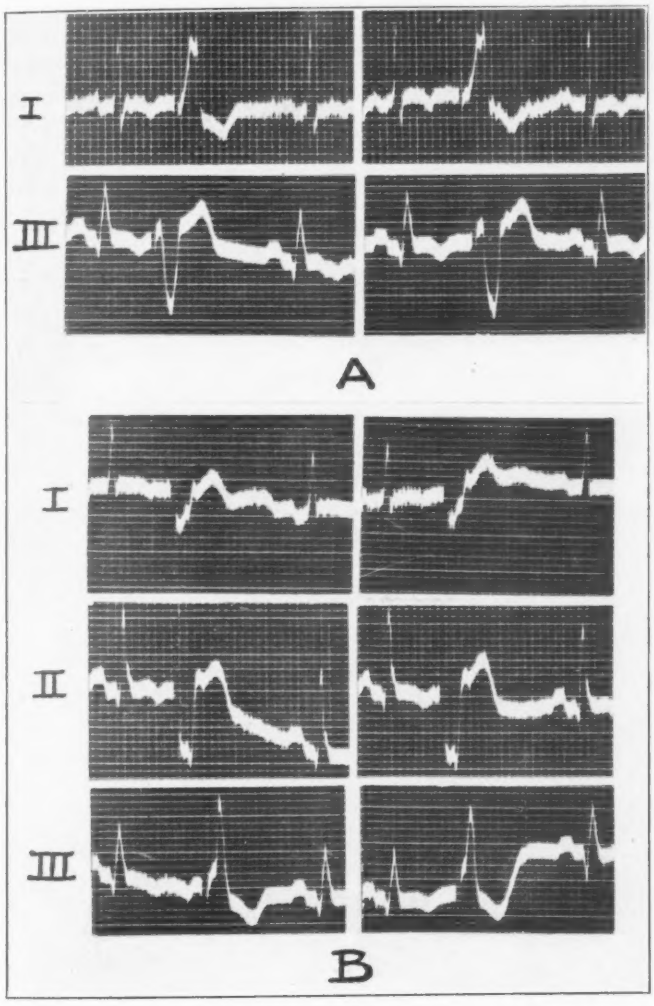

Fig. 2.—*A*. Leads I and III recorded during stimulation of the right ventricle. The curves on the right were secured two days after those on the left, and are precisely similar. *B*. The usual three leads recorded consecutively during stimulation of the left ventricle. The curves on the right were registered about fifteen minutes after those on the left. In Lead I the downward deflection of the premature beat measures 1.1 millivolt, but is largely lost in reproduction.

On June 13, the patient seemed sufficiently well to permit brief observations, and with his consent these were made. The pericardium was irrigated until the returning fluid was almost entirely clear, and the sac drained as thoroughly as possible by means of suction. The wound as

shown in Fig. 1 diminished in size as it penetrated the chest wall; it was actually funnel-shaped, so that the area of the heart's surface exposed to direct view was not large. It was very easy to stimulate the same point time after time without using landmarks other than the lower margin of the wound. A portable electrocardiograph was placed at the side of the patient's bed, and the usual attachments were made to the arms and left leg. Numerous attempts were then made to elicit premature beats by mechanical stimulation of the surface of the ventricle (tapping, pinching, etc.) but these were fruitless. We then connected an ordinary type of stimulating electrode to the secondary cell of an inductorium, so arranged as to deliver single break shocks upon opening a switch, and placed the points (separated by an interval of approximately 2 mm.) upon the surface of the heart. The strength of the current was not

Fig. 3.—Post-mortem photograph of the heart in situ, with the pericardium reflected. The white disc on the anterior surface lies upon the area actually stimulated; the arrow points to the level at which the posterior electrode was applied, but the actual point of stimulation is not shown.

actually measured; it was sufficient to produce a muscle-twitch when applied to a motor point on the normal moist skin.

One of us kept the electrodes applied to the heart and signalled to the nurse when stimuli were desired; the other watched the movements of the string shadow upon the face of the camera and photographed the beats when it was clear that the contact was satisfactory. The leads were recorded in sequence, not simultaneously. Numerous records were secured, of which only two are reproduced in Fig. 2*A*. It should be emphasized that the electrodes were removed and reapplied many times; the ectopic beats were precisely similar in all records.

Two days later it was possible to repeat these procedures; in addition, we had prepared electrodes to pass around the curve of the heart's left

border and stimulate the posterior surface. In appearance, these were not unlike the figure 5 without its top bar, or the lower half of the letter S. The extreme tip only was exposed, the remainder of the wire being covered in such a way as to permit its sterilization. With considerable difficulty this electrode was inserted through the wound and rotated in such a way as to bring its point against the posterior aspect of the heart a short distance above the apex. In this attempt, as in the earlier one, it was possible to be sure of the point of stimulation with considerable exactness, since adhesions had formed between the lower part of the pericardium and the heart, and the electrode was simply placed as far toward the apex as possible. The electrodes were withdrawn and reinserted four times, and the ectopic beats resulting from each procedure were identical. They are shown in Fig. 2*B*.

After death, the two areas used for stimulation were identified and marked through the same wound before the chest was opened. The anterior wall of the thorax was then removed; markers were placed to indicate the points of stimulation, and a photograph was taken (Fig. 3). The white disc marks accurately the spot upon the right ventricular surface that was used; the white arrow points merely to the approximate location of the stimulus on the left ventricle, as the electrode points were actually behind the heart. Long needles were then inserted deeply through these two spots, at right angles to the surface, and the heart was opened. The anterior needle was found to have entered the right ventricular cavity approximately 2 cm. from the interventricular septum and 3 cm. from the apex; the posterior one had entered the left ventricular cavity approximately 1.5 cm. from the septum and 4 cm. from the apex. These points apparently do not correspond accurately with any of those used by Barker and his coworkers; the one on the right ventricle lies between their points 6 and 9, while that on the left ventricle is apparently a little nearer the base than their point 12, but not so high as their point 11; it lies between their 3 and 12 and slightly higher than either. However, it would be obviously almost impossible to use points in exactly corresponding locations in two consecutive human hearts, and it is quite sufficient for the purpose of this report to know that the stimulated points lay on the lower portions of the right and left ventricle respectively. The curves derived from stimulation of these areas are to be compared with those shown in Figs. 7*A*, 7*B*, and 8 of their paper.

It is clear that the premature contractions induced by stimulation of the right ventricle in our patient are similar in all important respects with those registered by Barker, Macleod and Alexander from stimulation of the corresponding area in their patient (their points 6 and 8). In both cases, the curves are discordant, the chief initial deflections being upward in Lead I and downward in Lead III, and the terminal deflections are opposite in direction to the initial ones.

The deflections resulting from stimulation of the left ventricle in our patient, however, differ from those obtained from the earlier case in one respect; we consistently obtained discordant curves, the exact reverse of those from the right ventricle; that is, the chief initial deflections were downward in Lead I and upward in Lead III. In the first reported case, however, (1) concordant curves were obtained from all points on the apical portion of the left ventricle, and curves similar to ours from only one point (their point 1) higher toward the base. There are several possible explanations for this difference, but it is unnecessary to pursue the inquiry, since the important deductions seem clear.

Stimulation of the right ventricle in our patient, as in theirs, yielded discordant curves of which the chief initial deflections were upward in Lead I; stimulation of the left ventricle in both cases yielded complexes of which the chief initial deflections were downward in Lead I. The precise and extensive observations of Barker and his collaborators are confirmed in their most important respect by these very limited observations, and the conclusions drawn from their curves are strengthened by the ones here published.

SUMMARY

Premature contractions evoked by electrical stimulation of one spot upon the right ventricle and one upon the left ventricle of a partially exposed human heart have been recorded in the three standard leads of the electrocardiogram. These were not taken simultanously, but consecutively.

We are able to confirm the observations of Barker, Macleod and Alexander, who first showed that premature contractions derived from stimulation of the right ventricle have the chief initial deflection upward in Lead I, while those from stimulation of the left ventricle have the chief initial deflection downward in Lead I.

These records are published merely as confirmation of their work, which has hitherto rested upon curves obtained from a single case.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING LIGATION OF THE CORONARY ARTERIES OF THE DOG*

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EVER since the perfection of the electrocardiogram and its employment in the study of cardiac disease, clinicians have had a keen interest in establishing correlations between abnormal electrocardiograms and types and degree of cardiac injury. Although knowledge of the mechanism of production of the T-wave has been incomplete, yet the clinical importance of significant inversions of the T-wave in prognosis was conclusively established by Willius. One of us[1] undertook, in 1926, a careful anatomicopathological study of the hearts of 120 subjects who had come to necropsy, and who had exhibited significant inversions of the T-wave in life. It was hoped that certain inversions of the T-wave might be correlated with lesions demonstrable by anatomical or pathological means and possibly with certain types or situations of these lesions. This investigation, although in the main disappointing, indicated that with the exception of myocardial infarction, significant T-waves were not to be explained by lesions in the myocardium as demonstrated by ordinary pathological methods.

In addition, this investigation, coupled with clinical observations, led to the hypothesis that T-wave negativity could result from injury to the myocardium, the result of strain predominantly of either the right or the left ventricle. Furthermore, it seemed evident that such strain need not be manifested in the myocardium, except as hypertrophy, and at times as dilatation of one or the other ventricles. These conclusions were substantiated by the investigations of Barnes and Whitten.[2, 5] In addition, it was established that inversions of the T-wave were specific for the ventricle that was subjected to excessive strain; strain predominantly of the left ventricle was associated with inversion of the T-waves in Lead I or Leads I and II; strain predominantly of the right ventricle, with inverted T-waves in the combined Leads II and III. It was pointed out that these conclusions were in harmony with the experimental observations of Daly and Otto.

Barnes and Whitten[3, 6] also found that coronary occlusion and acute myocardial infarction produced characteristic modifications of the R-T and S-T components of the electrocardiogram, by which one could predict whether the infarction involved the posterior basal portion of the left ventricle and the adjacent interventricular septum, on the one hand, or the anterior portion of the left ventricle and apex on the other. This localization was possible because infarction in the poste-

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rior basal portion of the left ventricle produces electrocardiographic changes which are the exact reverse of those produced when the infarction involves the anterior and apical portions of the left ventricle.

These observations clearly suggest, if one may judge from the changes observed in the RS-T component of the electrocardiogram, that the heart of man is oriented to the conventional leads of the electrocardiogram in such a way that the electrical forces existent when acute infarction involves the posterior basal portion of the left ventricle are opposed to those present when acute infarction of its anterior and apical portion occurs. They indicate, further, that the right ventricle as a whole produces electrical forces which act on the T-wave in a manner opposite to those produced in the left ventricle, at least in its apical and anterior portion. The conception can be entertained that the opposition of electrical forces produced in the right and basal portions on the one hand, and in the apical and left portions on the other hand, in the heart of man determines the form of the RS-T segment and the direction of the T-waves. This conception is supported by experiments on the dog's heart, showing that injury to one ventricle produces effects on the electrocardiogram opposite to those produced by injury to the other ventricle. In axial leads it has been shown that a negative effect on the T-wave is produced by cooling the left ventricle,[8, 13, 20, 24] freezing the right ventricle,[13] ligation of the right coronary artery,[14] acute right ventricular strain,[7] stimulation of the right accelerator nerve,[15] and injection of alcohol (95 per cent) into the right ventricle.[16] A positive effect on the T-wave was produced by cooling the right ventricle,[8, 13, 20, 24] freezing the left ventricle,[13] ligation of the circumflex branch of the left coronary artery,[14] acute left ventricular strain,[7, 12] stimulation of the left accelerator nerve,[15] and injection of mercuric chloride or silver nitrate into the right ventricle.[8] A high take-off of the R-T component of the electrocardiogram was observed following injection of mercuric chloride,[8] silver nitrate[8] or alcohol (95 per cent)[16] into the left ventricle, whereas a low origin of the S-T component from the S-wave occurred when these substances were injected into the right ventricle.

Smith's[18, 19] investigations led him to conclude that in the dog the modifications of the electrocardiogram characteristic of infarction were produced experimentally only by ligation of the branches of the left coronary artery. Parkinson and Bedford,[17] in a consideration of their electrocardiographic studies of coronary occlusion, concluded that "all available evidence points to the fact that it is occlusion of the left coronary artery or its branches which produces characteristic T-wave changes." Katz,[10] in his review of the literature, reached the conclusion that inverted T-waves "occur in coronary involvement only when the left coronary artery is affected either clinically or experimentally." Barnes and Whitten's[6] work established conclusively the

fact that infarction produced by occlusion of the right coronary artery of the human being produced as characteristic a change in the RS-T wave as did occlusion of the left coronary artery. Otto,[14] using an axial lead, found that ligation of the circumflex branch of the left coronary artery of the dog (distributed exclusively to the left ventricle) increased the positivity of the T-wave; ligation of the right coronary artery (supplying the right ventricle) caused increased negativity of the T-wave, whereas ligation of the anterior descending branch of the left coronary artery (about equally distributed to the right and left ventricles) produced effects partially characteristic of each of the first two types of ligation.

PURPOSE AND METHOD OF STUDY

The present study represents a further investigation of the effects of ligation of the branches of the coronary arteries of the dog that go, respectively, to the right and to the left ventricle on the RS-T component of the electrocardiogram, using the standard electrocardiographic leads. Its chief object was to determine the difference between the electrocardiographic tracing before and after ligation of the right and left coronary vessels, and to see to what extent such changes as occurred could be compared with the change known to occur in the electrocardiogram exhibited by man following infarction. It seemed important to use all three conventional electrocardiographic leads, inasmuch as it is impossible to predict the changes in the T-wave which will occur in Leads I and III from a study of the changes of the T-wave observed in axial leads. Certainly by using the three conventional leads, one is better able to compare the changes obtained with those observed in the electrocardiogram of man.

The following method was employed in these experiments: Dogs were anesthetized with ether; the thorax was surgically prepared, and a tracheal cannula was introduced for maintenance of positive pressure. The left intercostal spaces were exposed, and the thorax was opened through the fourth left intercostal space. The adjacent ribs were forcibly separated by a retractor, permitting good exposure of the heart. The pericardium was incised, and, if desired, the coronary vessels were ligated. No attempt was made to exclude the vena comites from the ligature. The heart was allowed to fall back into the pericardial sac, but the pericardium was not closed by suture. The thorax was then closed.

Electrocardiograms were taken before an anesthetic was given, and in most instances both before and immediately after operation while the dog was anesthetized. No attempt was made to determine the blood pressure at the time the electrocardiograms were made. Electrocardiograms made immediately after operation actually were taken about twenty minutes after the coronary branches were ligated. This time was consumed in closing the thorax and carrying the animal to a separate room to make the electrocardiogram. Electrocardiograms were then made on the afternoon following operation, on the first and second days after operation, several times in the first two weeks, and after that at irregular intervals, until the dog died or was killed. Necropsy was performed after death in all instances which have been included in arriving at conclusions.

Before describing the results it is important to comment on certain features of the electrocardiograms of dogs. First of all, so far as the T-waves are concerned, they differ from those encountered in work with human beings. The most striking difference is the extreme variability of the T-waves in the normal electrocardiogram of the dog. The T-waves may be negative in Lead I, in Leads I and II, or even in Leads I, II and III in the normal dog. Furthermore, it appears that the same procedure may produce in the T-waves of a dog of which the T-wave was normally positive in Lead I, changes that are different from those obtained when the T-wave was originally negative in Lead I. So it appears that to compare the results of similar experiments it is essential to know the nature of the T-waves before the experiment is begun. Serial tracings following operation are essential if one is to compare the results with those obtained in studies of man following coronary occlusion. It is necessary to understand wherein the coronary circulation of the dog differs from that of man.[11, 21]

The literature dealing with the electrocardiographic effects of experimental obstruction of the coronary arteries of the dog is often lacking in data relating to control experiments. In our control experiments, which will be considered first, we duplicated every step of the ordinary experiment except that the coronary arteries were not molested. In one control experiment, the pericardium was vigorously manipulated.

Control experiment 1.—The electrocardiogram before anesthesia contained a sharp, positive T-wave in Lead I (Fig. 1, dog 1). The pericardium was opened in the usual manner, the heart was lifted out of the pericardial sac, but ligatures were not placed about the coronary arteries. The afternoon following operation, a deep, abrupt, negative T-wave was present in Lead I; T_2 was now sharply negative, and T_3 was exaggerated and positive. On the fourth day, positive T-waves appeared in Leads I and II, continued to increase in height with elevation of the R-T segment until the twenty-fifth day, and then disappeared. Then the T-waves in Leads I and II became inverted and remained so until the eightieth day, after which the dog was killed.

In study of dog 2, subjected to a similar operative procedure, and in which the T-wave of the electrocardiogram was sharply positive in Lead I, similar negativity of the T-waves in Leads I and II appeared, and T_3 became sharply positive in Lead III immediately after operation and remained so until the death of the dog one day after operation. In the electrocardiogram, taken under ether following operation, no significant change in the level of take-off of the T-wave from the R- or S-wave occurred, but the R-T segment in Lead II showed a distinct, negative troughlike effect.

In a like experiment on dog 3 (Fig. 2) of which the tracing taken before the anesthetic was given contained a positive T-wave of very low voltage in Lead I, negativity of the T-waves following opening of the pericardium and manipulation of the heart did not occur, but there did appear increasing positivity of the T-waves in Leads I and II, which became greatly exaggerated on the ninth day after operation. In the tracings of this dog, taken immediately after operation under ether, changes were not observed in the levels of the RS-T segment. The T-waves in the tracing taken forty-two days after operation assumed the same direction as those in the original preoperative tracings.

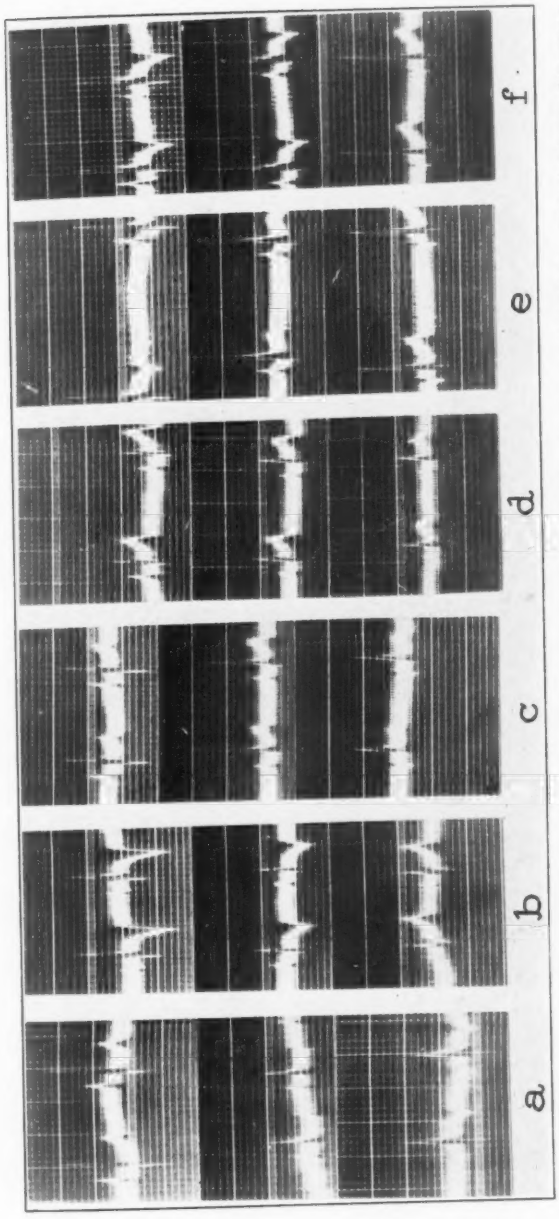


Fig. 1.—Dog 1. The pericardial sac was opened but the coronary arteries were not ligated. The electrocardiograms included here were taken: *a*, five days before operation; *b*, in the afternoon following operation; *c*, four days after operation; *d*, nine days after operation; *e*, fifty-four days after operation; *f*, seventy-two days after operation.

Necropsy.—Dog 1 was killed five and one-fourth months after operation. The pericardium was adherent over the basal three-fourths of the heart. There were no pericardial adhesions about the apex and anterior half of the left ventricle. The myocardium, the endocardium and the valves were normal.

Dog 2 died one day after operation. The pericardium had been incised. The coronary vessels were normal and not obstructed. There was no evidence of myocardial infarction and there was no cardiac hypertrophy. The valves and endocardium were normal.

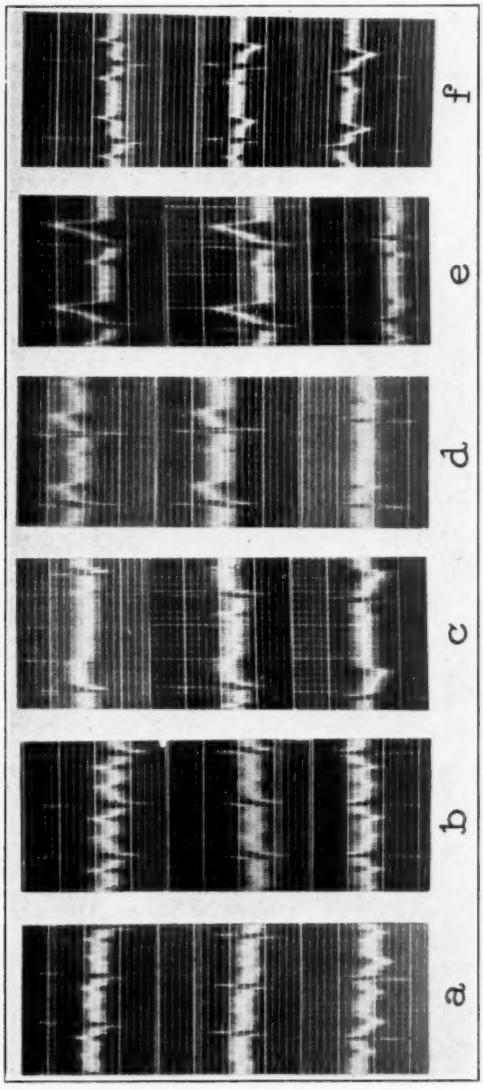


Fig. 2.—Dog 3. The pericardial sac was opened, but the coronary vessels were not ligated. The electrocardiograms were taken as follows: *a*, five days before operation; *b*, immediately before operation under ether anesthesia; *c*, afternoon after operation; *d*, five days after operation; *e*, nine days after operation; *f*, forty-two days after operation.

The pericardial sac of dog 3 had been opened, but the coronary vessels had not been ligated. The pericardium was adherent over the basal three-fourths of the heart. The apex and anterior half of the left ventricle were free of pericardial adhesions. There was no evidence of myocardial infarction. The valves and endocardium were normal.

Control experiment 2.—In the electrocardiograms of dog 4, the T-wave was nega- in Lead I and positive in Lead III in the tracing taken before operation. Here, in one instance, in which the pericardium was opened but the coronary arteries were not molested, the T-wave became positive in Leads I and II; in Leads II and III the T-waves became exaggerated on the tenth day (Fig. 3, dog 4). The electrocardiogram returned essentially to normal on the forty-third day and remained so until the dog was killed. The electrocardiogram of dog 5, taken before operation showed T-waves similar to those observed in the electrocardiogram of the fourth dog. In the electrocardiograms of dog 5 taken after the same type of experimental procedure as carried out on dog 4 the increased positivity of the T-waves in Leads II and III appeared, but the T-wave in Lead I never became positive. The tracing returned

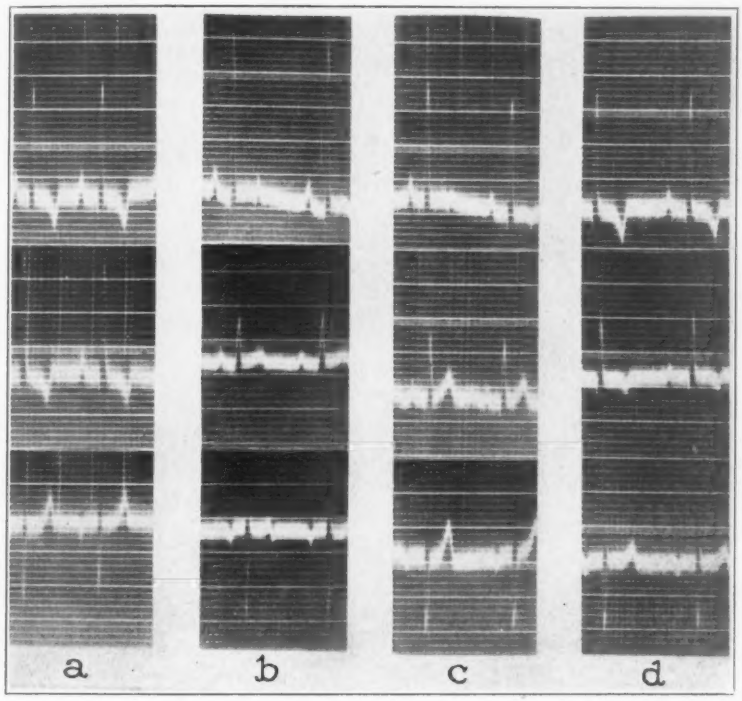


Fig. 3.—Dog 4. The pericardium was opened, but the coronary arteries were not ligated. The electrocardiograms were taken as follows: *a*, four days before operation; *b*, four days after operation; *c*, ten days after operation; *d*, forty-three days after operation.

essentially to normal on the sixteenth day after operation and remained so until the dog was killed (Fig. 4, dog 5).

Necropsy.—Dog 4 was killed two and a half months after operation. The pericardium had been opened, and was slightly adherent over the right ventricle and the upper posterior third of the left ventricle. There was no evidence of myocardial infarction. The endocardium and valves were normal.

Dog 5 was killed ten months after operation. The pericardium had been opened and was adherent by fine bands over the right ventricle and the adjacent anterior fourth of the left ventricle. Careful study of the heart revealed no evidence of myocardial infarction. The endocardium and valves were normal.

Control experiment 3.—Another type of control experiment was performed in which the pericardium was not opened, but in which the pericardial ligaments were severed and the heart was vigorously manipulated (dog 6). Negative T-waves of

low amplitude were present in all three leads in the normal preoperative tracing. There was no change in the RS-T levels in the electrocardiogram taken immediately after operation under ether. The T-wave in Lead I became positive on the afternoon following operation and remained so until the eleventh day after operation. The T-wave in Lead II was positive on the fourth day, was positive and exaggerated on the fifth day, and negative on the ninth day. The tracing returned to normal on the fifteenth day after operation.

Necropsy.—Dog 6 was killed two months and five days after operation. There were no pericardial adhesions. The myocardium, endocardium and valves were normal.

COMMENT ON CONTROL EXPERIMENTS AND THEIR RELATION TO LIGATION EXPERIMENTS

1. Sharp, deep inversions of the T-waves may follow opening of the pericardium and manipulation of the heart without ligation of any

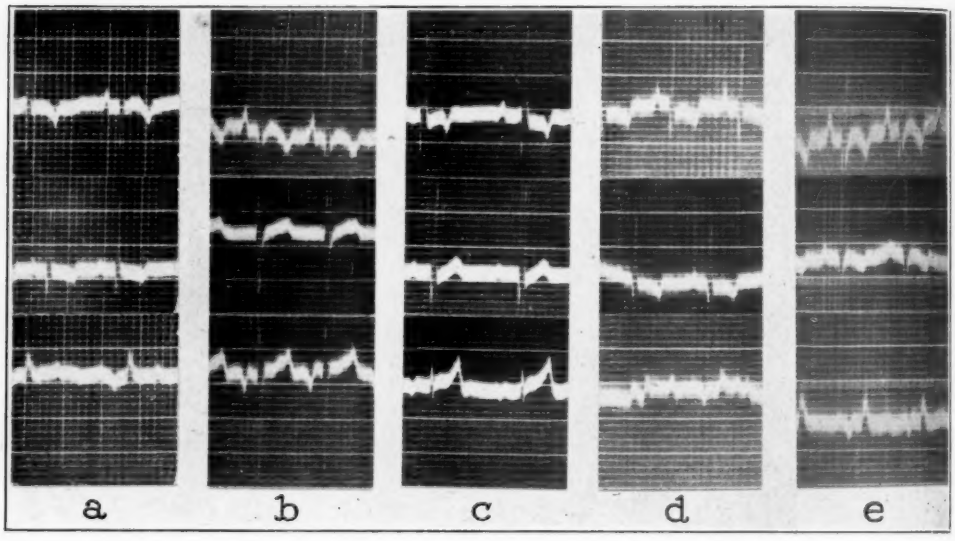
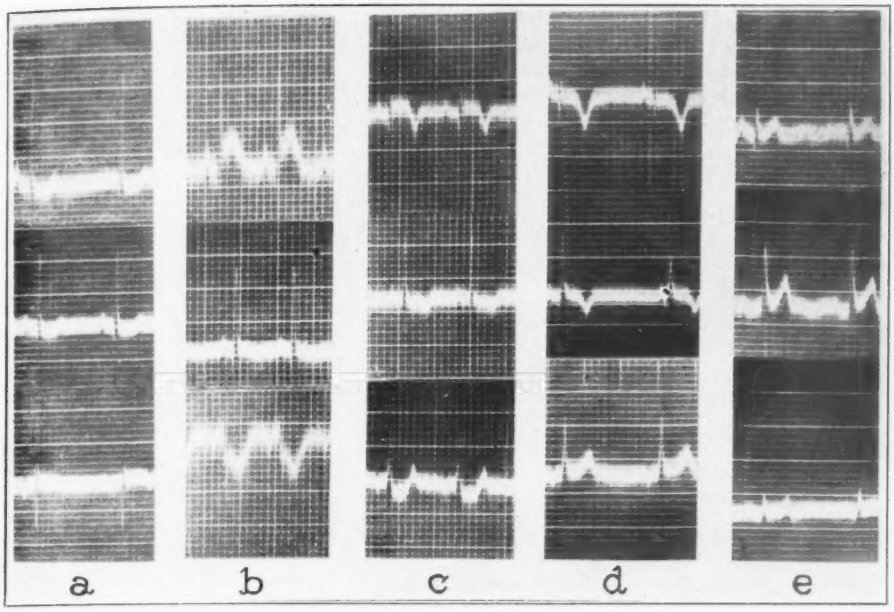


Fig. 4.—Dog. 5. The pericardial sac was opened but the coronary arteries were not ligated. The electrocardiograms were taken as follows: *a*, before operation; *b*, the afternoon following operation; *c*, seven days after operation; *d*, sixteen days after sixteen days after operation; *e*, seven and three-fourths months after operation.

coronary vessels. Under the conditions of our experiments it is evident that reversal of the direction of the T-waves only cannot be considered a manifestation of the effects of coronary obstruction.

2. There is a late stage in which T-wave negativity is replaced by positive T-waves which may arise from the descending limb of the R-wave and become greatly exaggerated. This change usually occurs in the combined Leads I and II or II and III, and is transitory in character, occurring from the fourth to the twenty-fifth day, although it may begin earlier and last longer.

3. There is more tendency for the T-waves to become reversed in direction and to maintain the reverse direction in the final electrocar-



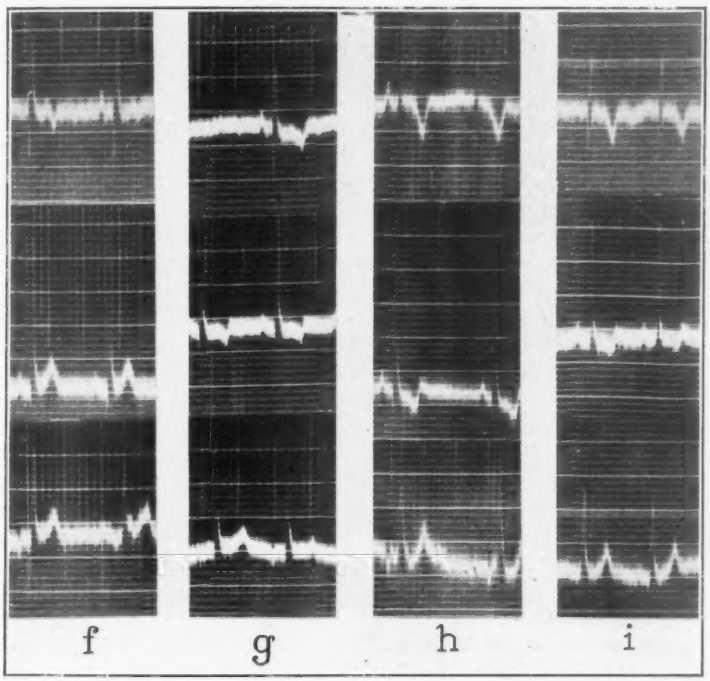


Fig. 5.—Dog 7. Ligation of the circumflex division of the left coronary artery. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation with the dog under ether anesthesia; *c*, the afternoon following operation; *d*, two days after operation; *e*, eleven days after operation; *f*, thirteen days after operation; *g*, twenty-two days after operation; *h*, ninety-five days after operation; *i*, two hundred seventy-five days after operation.

diograms of dogs in which the T-wave is sharply upright in Lead I in the original tracing. In dogs in which the T-wave in Lead I is negative in the tracing taken before operation, there is a distinct tendency for the tracings to return to normal after the period during which the T-waves become positive and exaggerated, as has been described.

4. In these control experiments no significant modifications of the level and contour of the RS-T segment occur in the electrocardiograms taken under ether, immediately after operation or during the remainder of the day.

With this knowledge of the electrocardiographic changes produced by opening the pericardium and manipulating the heart, but not interfering with the coronary circulation, one is in a position to recognize the effects of ligation of the coronary arteries. First the effects of ligation of the branches of the left coronary artery will be considered.

Ligation experiment 1 (left coronary artery).—The posterior division of the circumflex branch of the left coronary artery of dog 7 was ligated. In the electrocardiogram taken immediately after operation, while the dog was still anesthetized, was seen the high origin of the T-wave from the descending limb of the R-wave, with marked positivity of the R-T segment in that lead (Fig. 5). In Lead III there is marked fusion of the S- and T-waves resulting from low take-off of the T-waves. In Lead II the T-wave has become almost iso-electric. In the tracing taken in the afternoon following operation, with the dog fully awake, a negative T-wave is present in Lead I with a persistently high take-off of the T-wave, or, in other words, an elevated R-T segment. The S-T segment in Lead III was still markedly depressed, but the T-wave in Lead III had become sharply upright. Auricular fibrillation was present one day after operation, and the RS-T segments in Leads I and III retained similar, although slighter, changes to those just described. The changes in the level of the RS-T segments disappeared after the first day. Then followed increased negativity of the T-wave in Lead I, which was interrupted by positivity and exaggeration of the T-wave first in Leads I and II, and later in Leads II and III. From the twenty-second day, until the dog was killed, negativity of T_1 and T_2, and positivity of T_3 persisted. One is tempted to consider the sharply negative T-wave in Lead I, and the sharply positive T-wave in Lead III, observed at the end of the experiment, as a manifestation of infarction, the exact counterpart of which is seen in the late stage of the electrocardiogram of man when the apical and anterior portion of the left ventricle is the seat of infarction.[3,6] However, these same changes were observed in the control experiments (Fig. 1); therefore an interpretation such as that suggested is open to doubt.

Necropsy.—Dog 7 was killed eleven months after operation. At necropsy, the pericardium was adherent over various portions of the right ventricle, but adhesions to the left ventricle were not present to any extent, except over the region of infarction. A large, white area occupied the posterior portion of the left ventricle, immediately adjacent to the posterior interventricular septum. This area had a maximal width of 1.5 cm. and extended from 0.75 cm. from the base almost to the apex. The adjacent portion of the right ventricle was not involved, and there was only slight involvement of the posterior interventricular septum. The cardiac muscle was completely replaced in this area by scar tissue which had a thickness of about 2 mm. The myocardium of the remainder of the left ventricle, and of the right ventricle, was normal. No gross abnormalities of the endocardium or valves were noted.

Ligation experiment 2 (left coronary artery).—In dog 8 a branch of the circumflex division of the left coronary artery supplying the posterior and basal portion of the left ventricle was ligated. Here again was obtained a high origin of the T-wave from the R-wave, with a positive, convex, R-T component following operation (Fig. 6). There was slight upward convexity of the R-T segment in Lead II. In Lead III there was fusion of the S- and T-waves, with low origin of the T-wave from the S-wave in that lead. The subsequent changes were practically the same as those observed in control experiment 2 (Fig. 3).

Necropsy.—Dog 8 was killed ten months after operation. The pericardium was adherent, by scattered bands, over the entire right ventricle and the basal half of the left ventricle. The pericardium was very firmly adherent at the site of infarction, which was in the posterior basal portion of the left ventricle, 1.5 cm. from the base, and 1 cm. from the posterior interventricular septum. There was a depressed scar at the area of infarction measuring 1 by 1.5 cm., with a slightly greater area on the endocardial surface, and infarction involved the anterior papillary

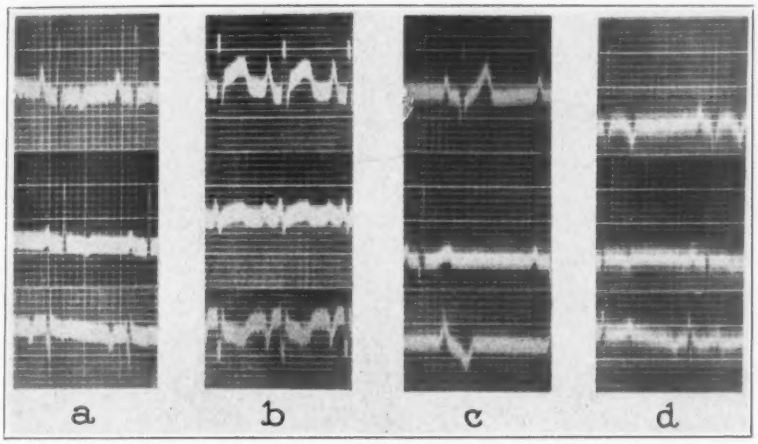


Fig. 6.—Dog 8. Ligation of a branch of the circumflex division of the left coronary artery. Electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation under ether anesthesia; *c*, ten days after operation; *d*, seventy-four days after operation.

muscle. At the central portion of this scar, practically the entire thickness of the left ventricle consisted of fibrous tissue. In the valves, endocardium, and remaining part of the myocardium, there were no gross abnormalities.

Ligation experiment 3 (left coronary artery).—In dog 9, the posterior descending branch of the circumflex division of the left coronary artery was ligated. In the electrocardiogram taken immediately after operation, while the dog was anesthetized, the T-wave in Lead I took its origin high on the R-wave; the T-wave in Leads I and II showed increased negativity, and there was marked fusion of the S- and T-waves in Lead III, with low origin of the T-wave from the S-wave (Fig. 7). These changes in the RS-T segment were present in the tracings taken in the afternoon following operation and one day following operation. The reciprocal relation of T_1 and T_3 is clearly shown in the fact that as T_1 became more negative, T_3 became more positive and acute. The dog died the second day after operation.

Necropsy.—Death of dog 9 resulted from hemorrhage from a small branch of the anterior descending division of the left coronary artery. A ligature was found about the posterior descending branch of the circumflex artery at a distance of about 0.7 cm. from the coronary sulcus. Injection of the circumflex branch disclosed an

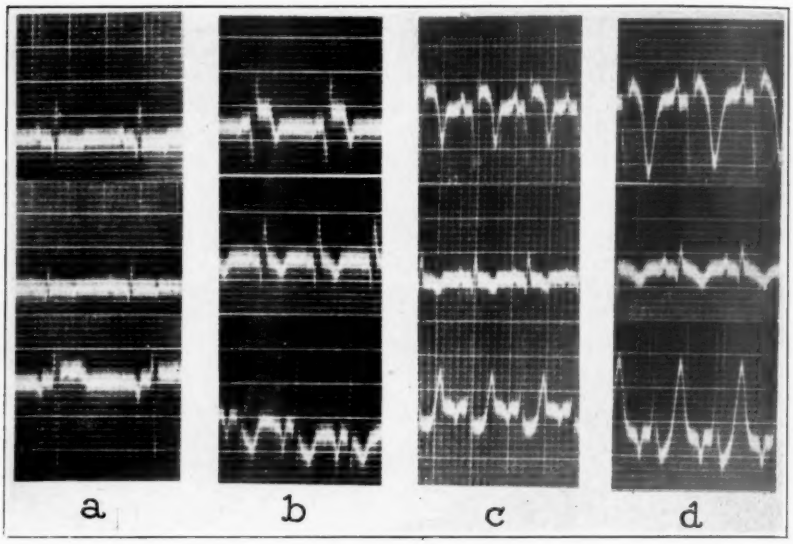


Fig. 7.—Dog 9. Ligation of the posterior descending branch of the circumflex division of the left coronary artery. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after the thorax was closed under ether anesthesia; *c*, the afternoon following operation; *d*, the day following operation.

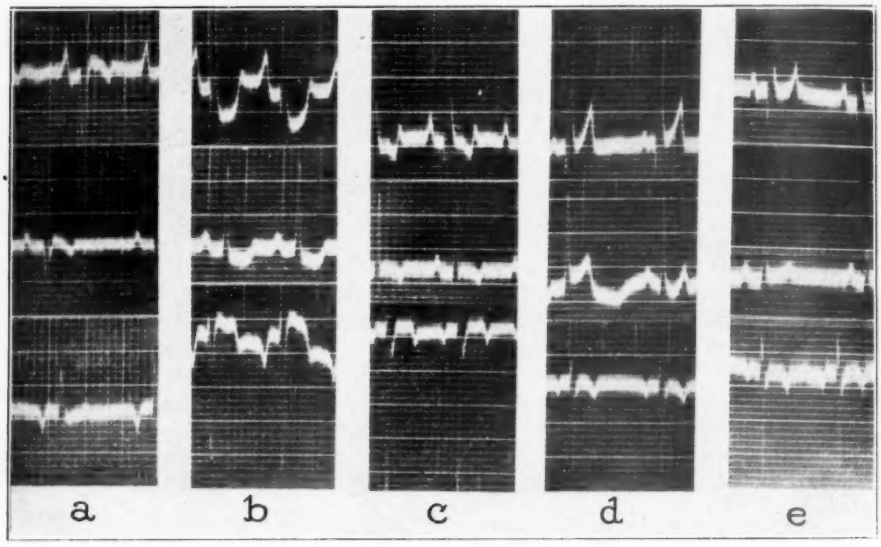


Fig. 8.—Dog 10. Ligation of two branches of the left coronary artery supplying the right ventricle. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation with the dog under ether anesthesia; *c*, the afternoon following operation; *d*, ten days after operation; *e*, two hundred one days after operation.

ischemic area below this point, to within 0.5 cm. of the apex. This area extended about 1 cm. anterior to the posterior insertion of the interventricular septum and occupied the posterior portion of the left ventricle. The endocardium and valves were normal.

In another dog (not numbered and not examined post-mortem) following ligation of two anterior branches of the circumflex division of the left coronary artery, an elevated convexity of the R-T segment occurred in Lead I, without a high take-off of the T-wave from the R-wave. Similarly, a depresed S-T segment occurred in Lead III, without a low take-off of the T-wave from the S-wave. These changes were present in the electrocardiogram taken on the day following operation and subsequently. There appeared on the third day a peculiar, convex, upward rounding of the R-T segment in Leads I and II, with slightly high origin of these segments from the R-wave. This is probably to be considered a preliminary step to the development of positive and exaggerated T-waves in those leads if the dog had lived.

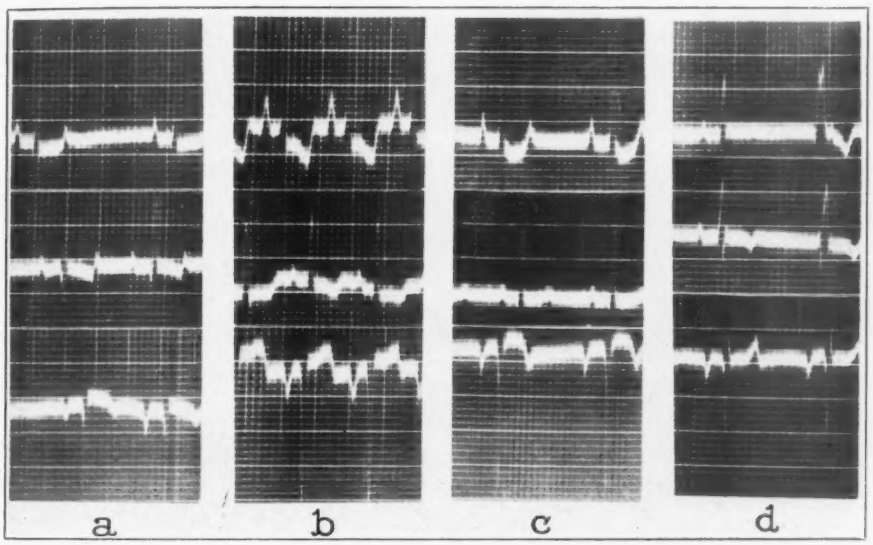


Fig. 9.—Dog 11. Ligation of a branch of the right coronary artery supplying the right ventricle. The electrocardiograms were obtained as follows: *a*, before operation; *b*, immediately after operation under ether anesthesia; *c*, the afternoon following operation; *d*, two days after operation.

In a control experiment in which all the steps of the experiment were carried out except ligation of coronary vessels, such changes in the R-T segments in Leads I and II appeared on the fifth day, and were followed by development of greatly exaggerated positive T-waves in those leads on the ninth day.

Ligation experiment 4 (right coronary artery).—In dog 10, two branches of the right coronary artery, supplying the middle portion of the right ventricle, were ligated. In the electrocardiogram taken immediately after the thorax was closed, with the dog under ether, we observed marked fusion of the S- and T-waves in Lead I with very low origin of the T-wave in that lead (Fig. 8). There was slight depression of the S-T segment in Lead II. The S-T segment in Lead III was markedly positive, with an upward rounded contour. This change was present, although in a much smaller degree, in the tracing taken on the afternoon following operation. Then the transitory phase of positive, exaggerated T-waves, with elevated take-off in Leads I and II, appeared, as were observed in control experiments. However, in this experiment, the exact reversal of the T-waves in the final tracings, as

compared to the original tracing, persisted to the end. We did not see this in control experiments in which we started with a negative T-wave in Lead I (Figs. 3 and 4). Inasmuch as the final electrocardiographic changes in this dog were such as would be observed in the late stage of infarction involving the posterior basal portion of the left ventricle in the heart of man, it is possible that they may be ascribed to infarction of the right ventricle. However, one is prevented from positively attributing them to infarction when it is recalled that such a reversal of the direction of the T-waves was obtained in a control experiment in which the T-wave was positive in the original tracing (Fig. 1).

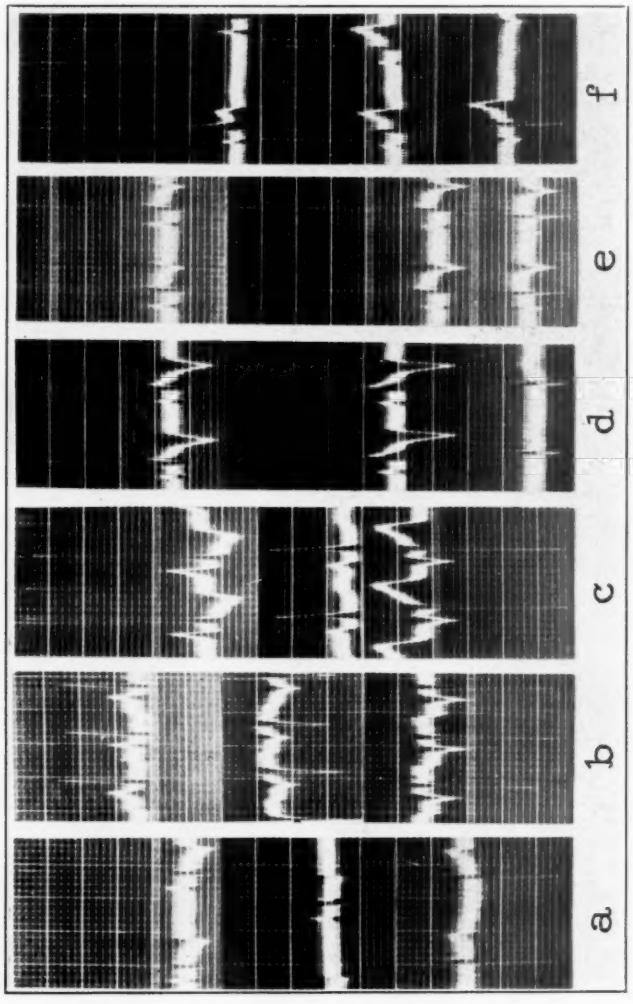


Fig. 10.—Dog 12. A branch of the right coronary artery, supplying a portion of the right ventricle, was ligated. Electrocardiograms were obtained as follows: *a*, before operation; *b*, before operation under ether anesthesia; *c*, immediately after operation under ether anesthesia; *d*, one day after operation; *e*, five days after operation; *f*, nine days after operation.

Necropsy.—Dog 10 was killed eight months after operation. At necropsy, pericardial adhesions were observed across the base of the right ventricle. The middle portion of the right ventricle was the seat of infarction, and was grayish in color. The infarct began about 0.5 cm. from the base, and spread out over a fan-shaped area, toward the apex of the right ventricle. This area was thinned. The fibrosis was largely confined to the epicardial half of the myocardium. The left

ventricle was thickened and apparently hypertrophied. The valves and endocardium of the remaining portion of the heart were normal.

Ligation experiment 5 (right coronary artery).—In dog 11, a branch of the right coronary artery to the right ventricle was ligated. In the electrocardiogram taken before operation there was slight depression of the S-T segment in Lead I, and slight elevation of it in Lead III (Fig. 9). In the electrocardiogram taken immediately after operation the depression of the S-T segment in Lead III was likewise accentuated. These changes persisted in lesser degree in the electrocardiogram taken in the afternoon following the operation. Two days after operation there was marked negativity of the T-wave in Lead I, and the T-wave in Lead III had become positive and exaggerated. The dog died four days after operation.

Necropsy.—Dog 11 died on the fourth day after operation. At necropsy, a ligature was found about the branch of the right coronary artery in the mid-basal portion of the right ventricle. There was a bluish discoloration of the pericardium spread out over the surface of the right ventricle, distal to this ligature, measuring 2 by 4 cm. The corresponding area on the endocardial surface had a bluish-red appearance. This was found to be an area of acute hemorrhagic infarction.

Ligation experiment 6 (right coronary artery).—A branch of the right coronary artery to the right ventricle was ligated in dog 12. In the electrocardiogram taken immediately after operation on the etherized dog, fusion of the S- and T-waves in Lead I, with depression of the S-T segment in that lead was seen (Fig. 10). The S-T segment had a high take-off in Lead III, with marked exaggeration and increased positivity of the T-wave in that lead. The R-T segment in Lead II was slightly depressed. The changes in the RS-T segment persisted definitely in Leads I and III in the afternoon, but disappeared thereafter. Then appeared, on the fourth day, an elevated take-off of the T-wave in all leads, which resulted, finally, in exaggerated positive T-waves in all leads. These positive T-waves persisted until the fifteenth day. It is well to recall that similarly exaggerated positive T-waves were to be observed in the tracings following control experiments, so that these changes are not regarded as a manifestation of the results of ligation of the coronary vessels.

Necropsy.—Dog 12 died one month after operation. On opening the pleural cavity it was found to be filled with blood-tinged fluid. There was an extensive, fibrinous exudate practically covering the heart, and that could be separated from it with difficulty. A grayish area occupied the middle portion of the right ventricle, and measured about 1.5 by 2 cm. This portion of the myocardium was markedly thinned. When viewed on its endocardial surface, the area was distinctly paler than the adjacent muscle. Microscopic section disclosed that this was an area of partially healed infarction. The endocardium, valves, and muscles of the remainder of the heart were not abnormal.

GENERAL COMMENT

In biological experiments it is always difficult to reproduce conditions in an animal that correspond exactly to those existing in man. In the dog the circulation, the distribution of the conduction system, the structure of the mediastinum, the angle that the heart makes with the various axes of the thorax, the influence of the vagus nerve, and the degree to which the right ventricle enters into the formation of the base of the heart may differ from those of man. It is not surprising, therefore, that the normal electrocardiogram of the dog differs so markedly from the normal electrocardiogram of man. It has been mentioned previously that the T-wave of the electrocardiogram of the

normal dog may be negative in Lead I, in Leads I and II, in Leads I, II and III, or in Lead III alone, and that the changes in the T-waves observed following our experiments varied according to the nature of the T-wave in the normal tracing.

The most important step in any investigation is the control experiment. We found that reversal of the direction of the T-waves could occur as a result of completion of all the steps of the experiment except ligation of the coronary vessels. So it became apparent that reversal of the direction of the T-waves following ligation of the coronary vessels could not be accepted unreservedly as a characteristic feature of infarction with the conditions under which our experiments were performed. This observation throws doubt on any investigation similarly performed in which the production of such a reversal of the direction of the T-waves is regarded as a manifestation of myocardial infarction in the dog. Moreover, the control experiments established the fact that the peculiar, exaggerated, positive T-waves produced usually in two leads, from the second to the twenty-fifth or fortieth day after operation, were not waves peculiar to experiments in which the coronary vessels were ligated. These results do not invalidate in any way the observations in man that reversal of the direction of the T-waves, and exaggeration and increased positivity of the T-waves, may occur as a result of coronary occlusion. However, it must be remembered that the conditions in coronary occlusion in man and those present in our experiments, at least in their later stages, are quite different. Under experimental conditions we have opened the pericardium, and whether we leave it open or suture it, there is likely to be a certain pericardial reaction leading commonly to adhesions over the various portions of the heart. We have to deal, then, with the effects on the electrocardiogram of inflammatory reactions, and what is probably more important, with the fact that adhesions occurring asymmetrically over the heart can modify the cardiac axes with reference to the various electrocardiographic leads. Moreover, the circulatory adjustments following obstruction of a coronary vessel in the face of the normal circulation of a dog cannot completely duplicate conditions following obstruction of a coronary vessel in the heart of man, the remainder of whose coronary circulation is usually seriously injured. Comparative anatomy suggests that the Thebesian circulation plays a more important part in the lower animals than it does in those higher in the biologic scale.[21]

After allowance is made for all the changes that are observed under the conditions of the control experiments, there is yet one important type of electrocardiographic change observed to occur after ligation of the coronary vessels. This has to do with modifications of the RS-T component of the electrocardiogram appearing immediately after operation, and usually disappearing in from a few hours to twenty-four hours after operation. This is most clearly manifested in Leads I and

III. Moreover, it is seen that these changes are characteristically different and opposite in type for infarction in the left and the right ventricle respectively. When a branch of the left coronary artery distributed exclusively to the left ventricle is ligated, producing infarction of the ventricle, in the tracing taken immediately after operation, origin of the T-wave from the R-wave in Lead I is high, and the R-T segment may take on a rounded, positive convexity. With this there may develop a very sharp, deep, negative T-wave in Lead I. In Lead III, on the contrary, there is fusion of the S- and T-waves with a low take-off from the S-wave, producing a trough-like depression of the S-T segment. If the dog fails progressively, and dies within twenty-four to forty-eight hours after operation, this change may persist to the end. However, if a branch of the right coronary artery is ligated, producing infarction in the right ventricle, in the tracing taken immediately after operation a high origin of the T-wave from the R-wave in Lead III is observed, producing a positive, convex, R-T segment in that lead, with or without negativity of the T-wave. In Lead I, fusion of the RS-T segment is observed, with a low take-off of the T-wave from the R- or S-wave, leading to a trough-like depression of the RS-T segment. It will be observed, also, that the T-waves in Leads I and III tend to act reciprocally; that is, as the T-wave in Lead I undergoes inversion, the T-wave in Lead III becomes positive, sharp, and exaggerated; whereas, when the T-wave becomes negative in Lead III, the T-wave in Lead I tends to become more positive and sharper. The changes observed in Lead II do not obey any definite or predictable pattern, and clearly indicate the advantages of including Leads I and III of the electrocardiogram in any study of the effects of experimental coronary occlusion.

Mention has been made of the fact that these changes in the RS-T components of the electrocardiogram disappeared in a few hours, except in an instance in which the dog progressively failed until its death on the second day after operation. At first glance, this might be considered as indicating that these changes were not due to myocardial injury. However, Otto[16] observed a similar rapid decrease in the degree of changes in the RS-T segment produced by injecting 95 per cent alcohol into the cardiac muscle. Smith[18] also observed that the increased prominence of the T-wave, observed immediately after ligation, was replaced in twenty-four hours by a sharply negative T-wave. It appears possible that the condition produced in the myocardium of the dog following coronary ligation or chemical injury results in changes in the RS-T segment of the electrocardiogram which undergo readjustments more rapidly than they do in the human heart. Were it practicable, at this point we should like to review for comparison the duration of the changes in the RS-T segment, observed in the electrocardiogram of man following myocardial infarction,[4, 17] as pointed out by Parkinson and Bedford[17] and by Barnes.[4] What is more important, probably, is the fact that those electrocardiographic changes

that occur independently of infarction, and observed in our control experiment, namely, reversal of the direction of the T-waves and their positive exaggeration in one or more leads, appear early, and they obscure the modifications in the RS-T segment.

This study clearly indicates that infarction in one ventricle produces electrocardiographic effects which are characteristic and opposed to effects produced by the other ventricle. The work of Eppinger and Rothberger,[8] and Otto,[14, 16] indicated that this was true for axial leads. Our investigations do not answer the question as to whether infarctions of various portions of the same ventricle of the dog produce dissimilar electrocardiographic changes. This question seems definitely answered in the negative by the findings of the investigators last mentioned.

Are these changes in the RS-T segment, following infarction, the result of electropotential forces of the right and of the left ventricle, which are antagonistic because the right ventricle occupies a right basal position, whereas the left ventricle constitutes the left and apical portion of the heart? Are they linked up with the fact that the conduction system to the right and left ventricles of the heart are separate, and that injury anywhere within the region supplied by one side of the conduction system produces a characteristic change? Or are these changes related, in some fashion, to the fact that injury in the region of the myocardium supplied by one coronary artery produces a characteristic electrocardiographic picture? It seems fairly certain that we can answer the last two questions in the negative by referring to the results observed in infarction in the heart of man. In man acute infarction at the posterior basal portion of the left ventricle produces changes in the RS-T segment that are characteristic, and that are opposed to those produced by infarction in the anterior and apical portions of the left ventricle.[4, 6] In man, also, the same branch of the conduction system supplies both regions of infarction, and the electrocardiographic changes are the same following acute infarction of the posterior basal portion of the left ventricle, regardless of whether it is supplied by the right or the left coronary artery.[6] A number of experimental observations seem to oppose the idea that infarction in the right ventricle of the dog produces opposite effects on the RS-T segment from infarction in the left ventricle, by virtue of the fact that the right ventricle occupies a basal position in the heart with reference to the left ventricle. The experiments of Eppinger and Rothberger, and of Otto, indicate that injury to any part of the left ventricle produces the same type of electrocardiographic change. In the injury to one ventricle, Eppinger and Rothberger found that when changes in the RS-T segment occurred they were all of a similar type, although differing in degree, and Otto arrived at a similar conclusion. It was found, also, that injury of the left half of the septum, no matter at what level, produced the same type of RS-T change as did injury of any other portion of the left ventricle, whereas, similar injury of the

right half of the septum produced an RS-T effect that was no different from that produced by injury of any portion of the right ventricle.[8] Moreover, Otto[14] found that ligation of the anterior descending branch of the left coronary artery supplying the anterior portion of both the right and the left ventricles, adjacent to the interventricular septum, produced electrocardiographic changes which partook partly of the character of those produced by injury of the left ventricle, and partly of those produced by injury of the right ventricle. The available evidence seems to indicate that so far as effects on the RS-T component of the electrocardiogram are concerned, the dog's heart may be conceived of as being divided by a plane fairly accurately separating the right and left ventricles. Such a separation does not appear to exist in the heart of man.[6]

Is cardiac dilatation essential to the production of fusion of the RS-T segment following experimental occlusion of coronary arteries of the dog? The transitory character of the changes in the RS-T segment which we obtained, and their tendency to persist until failure and death twenty-four to forty-eight hours after operation, might be in harmony with such an observation. Further experiments to induce cardiac dilatation following experimental obstruction of coronary vessels, and determination of the effects of these combined procedures on the RS-T segment of the electrocardiogram should throw light on this question.

The investigations of Feil, Katz, Moore and Scott[9] indicate that ligation of the descending branch of the left coronary artery alone does not produce modifications of the RS-T segment of the electrocardiogram characteristic of infarction, in dogs that are allowed to survive sixty-eight minutes or less after the coronary ligation. These investigators were able to produce such changes in the RS-T segment only if, in addition to ligation of the descending branch, they obstructed the inferior vena cava. They felt that the marked fall in mean blood pressure with followed obstruction of the vena cava, and the increasing anoxemia thus produced, were necessary factors in production of the changes in the RS-T complex in the electrocardiogram. In this connection it is well to recall that the descending branch of the left coronary artery in the dog supplies not only the anterior portion of the left ventricle, but the interventricular septum and the adjacent portion of the right ventricle as well. In axial leads, Otto noted that closure of the right coronary artery had a negative influence on the T-wave of the electrocardiogram; closure of the circumflex division of the left coronary artery had the opposite effect, and closure of the anterior division tended to produce both effects; that is, "the T-wave began before the complete ascent of S, yet its peak became more positive." He explained the latter result by the fact that the zone of discoloration which followed ligation of the descending branch occupied a position over the lower portion of the anterior interventricular groove and

apex, midway between the right ventricle above and anteriorly, and the left ventricle to the left and posteriorly. This might explain why Feil and others obtained changes in the RS-T segment characteristic of infarction of the right ventricle in some instances, due to involvement predominantly of the right and basal portion of the heart, and in other instances evidences of infarction of the left ventricle, due to involvement predominantly of the left and posterior portion of the heart. In other words, the area of ischemia in the dog's heart produced by ligation of the descending branch of the left coronary artery may be a relatively neutral zone. It may give rise to opposed electrical effects of right and left ventricular origin, making it somewhat difficult to obtain changes in the RS-T component characteristic of infarction. When such changes are obtained, they may not be constant in all animals.

CONCLUSIONS

1. Infarction of the right ventricle produced by ligation of branches of the right coronary artery in the dog induces characteristic changes in the RS-T component of the electrocardiogram. These changes are distinctly different from those following infarction in the left ventricle produced by ligation of branches of the left coronary artery.

2. These characteristic changes are best appreciated only when one studies Leads I and III of the electrocardiogram.

3. The changes in the RS-T segment observed following acute infarction of the left ventricle of the dog closely resemble the early changes in the RS-T segment following acute infarction of the anterior apical portion of the left ventricle of man.

4. The changes in the RS-T segment observed following acute infarction of the right ventricle of the dog closely resemble the early changes in the RS-T segment following acute infarction of the posterior basal portion of the left ventricle of man.

5. The reversal of the direction of the T-wave and the occurrence of exaggerated positive T-waves in one or more leads could not be considered to be a result of infarction, inasmuch as these same changes were observed to occur in similar experiments in which the same procedures were carried out except that no coronary vessels were ligated.

6. The available evidence indicates that so far as their effects on the RS-T segment of the electrocardiograms are concerned, the right and the left ventricle of the dog each acts as a unit. This behavior does not seem to be explained wholly by the fact that the right ventricle occupies a more basal position than the left ventricle.

7. Control experiments in evaluating changes following experimental occlusion of the coronary vessels in the dog are important.

8. It is impossible to secure strictly comparable conditions in myocardial infarction following experimental occlusion of the coronary vessels in dogs and following spontaneous closure of the coronary vessels in man.

9. The character and direction of the T-wave in the normal electrocardiogram of the dog differ from the same features of the normal electrocardiogram of man. The changes of the T-wave in the dog following identical experimental procedures appear to vary according to the character and direction of the T-wave in the normal electrocardiogram.

10. The last two conclusions probably explain why it is difficult to interpret, and probably not possible to reproduce, in dogs, the late changes in the electrocardiogram as seen in man following myocardial infarction.

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AURICULAR FLUTTER AND FIBRILLATION SHOWING VARYING BLOCK ASSOCIATED WITH CHEYNE-STOKES RESPIRATION*†

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IT IS well known that changes in sinus rate occur during Cheyne-Stokes respiration. The subject is fully discussed by Wenckebach and Winterberg.[1] Usually it is found that the sinus rate slows during the hyperpneic stage and speeds up during the apneic period. The change is due as a rule to a central action of the vagus, which alters the activity of the sinus node. We have found no notation in the literature of the appearance of block in Cheyne-Stokes breathing, either with sinus rhythm, auricular flutter or auricular fibrillation. For this reason an unusual case is described in which Cheyne-Stokes breathing occurred during sinus rhythm, auricular flutter and auricular fibrillation with, at times, striking variation, sometimes halving, of the ventricular rate during auricular flutter due to synchronous changes in A-V block paralleling the hyperpneic and apneic periods.

CASE REPORT

History.—S. G., aged thirty-nine years, married, was admitted to the Meyer House on January 28, 1931, complaining of dyspnea, cough, and insomnia of a month's duration with edema of the ankles for the past two days. There was a definite history of recurrent attacks of rheumatic fever at the ages of nine, eleven and fourteen years. In July, 1929, he suffered from an attack of streptococcus sore throat during which he complained of attacks of severe precordial pain. A diagnosis of pericarditis with effusion was made at this time.

On admission he was kept at rest in bed and given morphine. Fluids were limited to 1000 c.c. per day, and he was kept on a high caloric, high carbohydrate diet. He was also slowly digitalized and finally became fully compensated in about ten weeks, when he was discharged in relatively good condition. Two electrocardiograms were taken at this time (Fig. 1 *A* and *B*), showing notching of QRS and in the second record some prolongation of A-V conduction time, up to 0.22 sec.

On April 8, 1931, he was again admitted to the hospital in a state of advanced congestive heart failure. He was again put on a régime of rest, high carbohydrate diet and fluid restriction. Pantopon, gr. 1/3, was given when needed. Digitalis was given for a period of seven days and was then refused by the patient. During digitalis medication auricular fibrillation developed, which was followed by auricular flutter. Quinidine sulphate was administered over a period of five days, 2 grams in all being given, during which the mechanism was restored to the sinus rhythm.

Physical Examination.—The patient was an adult, white male of about forty years, well developed and well nourished. He was orthopneic, dyspneic, and had a characteristic mitral flush of the cheeks. His lips, tongue and ear lobes were cyanotic. The thyroid gland was not palpably enlarged. The veins of the neck were distended,

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pulsating and filled from below. The lungs presented dullness and crepitant râles at the bases. The apex beat was palpated in the sixth interspace, at the left anterior axillary line. There were a precordial heave and a systolic precordial purring thrill. The right heart border was percussed 4 cm. from the midsternal line and the left heart border in the left anterior axillary line. Presystolic and systolic murmurs

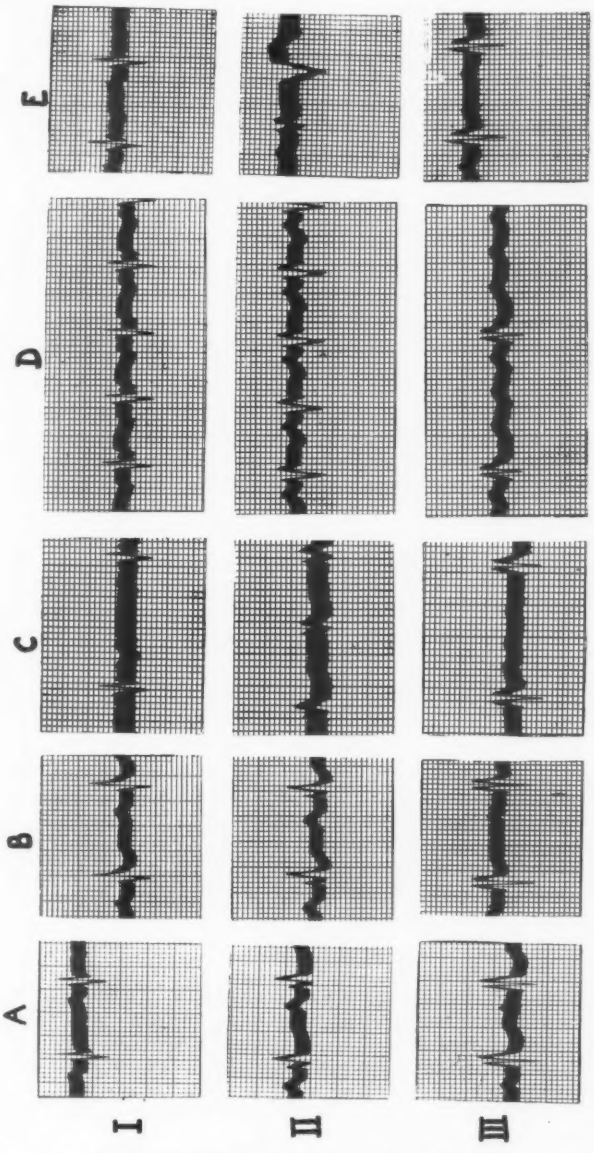

FIG. 1.—Segments from electrocardiograms taken on January 24, *A*; on February 2, *B*; on April 15, *C*; in the morning of April 28, *D*, Leads I and II during apnea and Lead III during hyperpnea; and on May 12, *E*.

were heard at the apex and a diastolic murmur was heard over the aortic area. The second aortic sound was louder than the second pulmonic. The liver edge was felt four fingerbreadths below the costal margin; the organ did not pulsate and was slightly tender. The flanks bulged and a fluid wave was elicited. Capillary pulsation, Corrigan pulse, and a Duroziez murmur were noted. The legs showed moderate pitting edema. The reflexes were not abnormal.

The diagnosis on admission was rheumatic heart disease, cardiac hypertrophy and dilatation, mitral insufficiency and stenosis, aortic insufficiency, sinus rhythm, Class III.

Progress.—The physical examinations showed essentially the same condition on both admissions. The progress of the first stay in the hospital has been summarized in the history. During the first stay in the hospital there was a persistent regular sinus rhythm and no evidence of Cheyne-Stokes breathing.

On the second entry on April 8 the patient was rapidly digitalized. The electrocardiograms on April 15 (Fig. 1 *C*) showed coarse auricular fibrillation, whereas on the previous day frequent premature contractions were demonstrated clinically. A sinus mechanism was restored in a few days. On April 18 he had a short attack of apnea, and three days later Cheyne-Stokes respiration set in which persisted until his death; a gallop rhythm was also noted at this time. During the same day he had an attack of severe orthopnea, vertigo, tinnitus, and motor aphasia. The next day he had a right-sided hemiparesis with hemianesthesia and right homonymous hemianopsia, with continuance of the aphasia. The neurological diagnosis by Doctor L. J. Pollock was "vascular accident to the internal capsule." The intracranial lesion progressively improved, and the pulse continued to be regular. On April 27, it was noted that the pulse was slow during the hyperpneic phase and rapid during apnea; this was confirmed by an electrocardiogram (Fig. 1 *D*) taken on the next day, which showed that the mechanism was a flutter of the auricles with 2:1 block during apnea and 4:1 block during hyperpnea. Later that afternoon another record was taken which showed coarse auricular fibrillation with varying block associated with Cheyne-Stokes respiration. Quinidine medication was started on April 29, a total of 2 grams having been taken by May 1, after which time it was refused. Electrocardiograms taken on May 9 and 12 (Fig. 1 *E*) showed a return to normal sinus mechanism with no respiratory variation of the rate as was previously noted, and only an occasional ventricular extrasystole.

The patient ran an afebrile course until April 22 when for a period of eight days there was fever, the highest level reached being 102° F. The temperature then subsided until May 6 when it started to rise and remained elevated, reaching the level of 105.4° F. at the end. The apneic periods became progressively longer and the pulse very thready. He died on May 15. A postmortem examination was not done.

Laboratory Data.—Roentgenogram of the chest showed the transverse heart diameter to be 20.5 cm. and the transverse chest diameter, 30.5 cm. A small amount of fluid in both costophrenic angles was present.

The basal metabolic rates were +50.2 per cent on February 11, and +13.0 per cent on February 14. Blood chemistry on January 29 showed sugar, 101 mg. per 100 c.c.; nonprotein nitrogen, 38 mg. per 100 c.c. On April 24, sugar was 95 mg. per 100 c.c.; nonprotein nitrogen, 43 mg. per 100 c.c.; creatinine, 2.1 mg. per 100 c.c. A blood culture was negative on two weeks' growth. Urinalysis showed four-plus albumin, occasional red and white cells, and coarsely granular casts. A blood count on April 9 showed R.B.C., 4,440,000; Hb., 75 per cent, and W.B.C., 8,200. On April 26 the W.B.C. count was 10,600. The blood pressure varied between 150/0 and 270/0 mm. Hg.

COMMENT

The electrocardiograms show definite evidence of intraventricular block of the so-called "aborization type" (cf. Fig. 1). The QRS is small in amplitude, prolonged to 0.12 of a second, and notched deeply. In Lead I it is chiefly directed downward; in Lead II, in most records, it is directed upward, but in Fig. 1 *D* it is mainly downward; in Lead III

the direction is more variable. The T-wave is small or not discernible, viz., in Fig. 1 *C* and 1 *E*; it is upright in Lead III and inverted in Lead I. In most instances the S-T segment is negative in all leads or at least in Leads II and III. The change from a sinus rhythm to coarse auricular fibrillation, then to auricular flutter and back to a sinus rhythm is shown in Fig. 1. A ventricular extrasystole is seen in Lead II of Fig. 1 *E*. The P-R interval is 0.20 sec. in Lead II of Fig 1 *A* and *E* and 0.22 sec. in Fig. 1 *B* indicating the presence in the latter record of first-stage A-V block.

The flutter record of Fig. 1 *D* was taken during Cheyne-Stokes breathing. Leads I and II during the apneic and Lead III during the hyperpneic stage. The flutter waves are clear and regular at a rate of

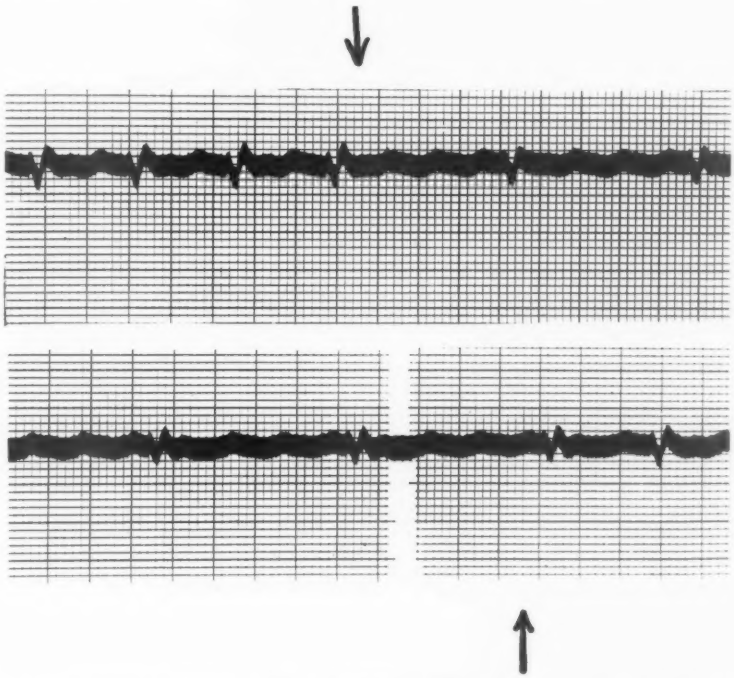

Fig. 2.—Electrocardiogram, Lead II, taken April 28, A.M., showing auricular flutter with transition from 2:1 to 4:1 block and back, during various phases of Cheyne-Stokes breathing. ↓ shows onset of hyperpnea, ↑ shows end of hyperpnea.

250 per minute. During apnea there is 2:1 A-V block; during hyperpnea the block is increased to 4:1. The transition from 2:1 to 4:1 block and back is shown in the two segments in Fig. 2 selected from a long strip of Lead II taken at the same time as the record in Fig. 1 *D*. It was observed that the transition from 2:1 to 4:1 block occurred when apnea ended and the transition from 4:1 to 2:1 block occurred when apnea began. The change in A-V block was unaccompanied by any change in the flutter rate.

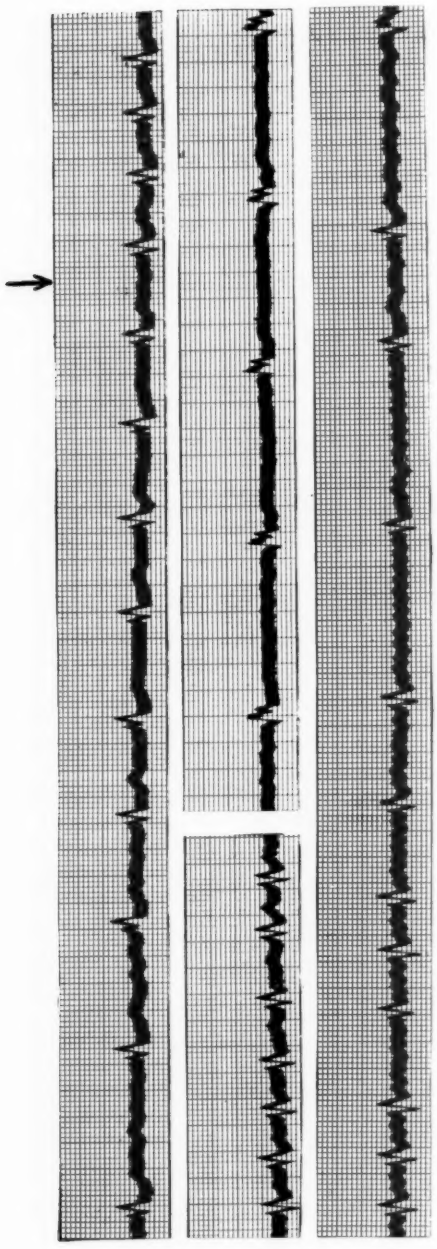

Fig. 3.—Electrocardiogram, Lead II, taken April 28, P. M. In upper strip is shown decrease in A-V block during the apnea, (↓ shows onset of apnea); the mechanism is a coarse auricular fibrillation. In middle two strips, is seen the development of complete A-V block during hyperpnea, the mechanism being coarse auricular fibrillation. In lower strip is seen increase in A-V block during hyperpnea, onset of which is shown by ↑. Note the change in the flutter waves from a double wave to a notch which eventually disappears.

The same afternoon a continuous record was taken during several cycles of Cheyne-Stokes breathing; a record of the respiratory activity being taken simultaneously with the electrocardiogram to time the changes in the latter more accurately. During this long record the auricles were alternating between coarse auricular fibrillation as in the two upper strips of Fig. 3 and auricular flutter as in the lower strip of Fig. 3. The lower strip shows the flutter rate to be 300. During the apneic phase (early part of strip) the flutter waves are split in two, and there is 2:1 and 4:1 block. When the patient began to breathe, the doubling of the flutter wave changed after a short lag to a notch which became less and less distinct at the same time the A-V block increased to 4:1 and 7:1 block. This change was not associated with any change in the flutter rate. In the middle strip is shown the coarse auricular fibrillation with the rapid irregular ventricular rate averaging 143 beats seen in apnea, and the slow regular ventricular rate of 45 seen during hyperpnea, which is probably a complete A-V block with the idioventricular rhythm located in the A-V node, as is borne out by the change in the appearance of the QRS complex. The auricular oscillations are irregular in spacing and amplitude and not very clear. In the top strip is shown the more gradual transition in A-V block as the apneic stage replaced the hyperpneic.

When the record of Fig. 1 *E* was taken, a long strip of Lead II was made during the Cheyne-Stokes breathing. The irregularity in breathing was less marked than when the records of Figs. 2 and 3 were taken, and no significant change in sinus rate or P-R interval was found.

This case is unusual in that Cheyne-Stokes breathing produced no cyclic changes in sinus rate nor, apparently, any cyclic change in the rate of auricular flutter and fibrillation. The variations in ventricular rate which occurred during the periods of auricular flutter and fibrillation were due to marked alterations in the A-V block. During the period of auricular flutter the block changed from 2:1 during apnea to 4:1 during hyperpnea in one instance; during a period of coarse auricular fibrillation complete A-V block developed in the hyperpneic period of Cheyne-Stokes breathing. The change in block synchronized with the change in the character of breathing. The increase in A-V block during the hyperpneic period can be explained by a spread of impulses from the hyperactive respiratory center to the closely adjoining cardioinhibitory center, an explanation which has been advanced to explain the sinus bradycardia during hyperpnea in Cheyne-Stokes breathing (Wenckebach and Winterberg[1]). On the other hand the increased A-V block may be due to some chemical change in the blood, such as the anoxemia and hypercapnia, which produce the cyclic modification in the respiratory center activity (Haldane[2]), acting simultaneously on the cardioinhibitory center. The studies of Resnick[3] on the effects of anoxemia on

A-V conduction would suggest that the chemical changes in the blood might produce their effect directly on the A-V node. The evidence is inconclusive as to which mechanism operated in this case.

SUMMARY

An unusual case is reported in which the A-V block accompanying auricular flutter and coarse auricular fibrillation varied markedly during Cheyne-Stokes breathing, in one instance leading to a complete A-V block during the hyperpneic stage. Hyperpnea in this case increased the A-V block and apnea decreased it without any apparent effect on the rate of flutter or fibrillation of the auricles.

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EXPERIMENTAL BUNDLE-BRANCH BLOCK IN THE CAT

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THE electrocardiographic distinction between right and left bundle-branch block in human beings has been associated with considerable confusion. The classification of Lewis and his coworkers,[1, 2] based largely upon their experimental work on dogs, found for a time almost universal acceptance. However, Fahr[3] in 1920, chiefly on theoretical grounds, came to the conclusion that electrocardiograms ascribed to right bundle-branch block by Lewis actually represented left bundle-branch block, and vice versa. Barker, Macleod and Alexander,[4] in a remarkable study of the excitatory process in an exposed human heart, developed evidence strongly suggestive of the latter view. More recently Mann[5] and Wilson, Macleod and Barker,[6] using entirely different methods, re-analyzed the original records of Lewis and came independently to a conclusion opposite to his.

Since most of the confusion is due to curves Lewis obtained by cutting or clamping the main branches of the bundle in dogs, we have repeated the work on cats.

METHOD

Nineteen cats were used, the anesthetic being sodium amytal injected intraperitoneally (75 mg. for an adult cat). Needle electrodes were placed under the skin and tied. The chest was opened, artificial respiration established and the whole heart exposed by slitting the pericardial sac; the control electrocardiogram being taken after this step. A cataract knife, the handle of which had been replaced by an oval shank of much smaller diameter, was used to produce the desired lesion.

In the first six experiments the knife was introduced into the ventricular cavity by way of the auricular appendage, while in the remaining thirteen it was inserted directly through the ventricular wall. Using the direct or ventricular route, the right branch was cut by inserting the knife through the anterior wall near its junction with the septum, just below the pulmonary cusps. After it was introduced a short distance into the ventricular cavity nearly parallel to the auriculoventricular groove, it was slowly withdrawn with the cutting edge directed against the septum so as to transect the main branch in its course to the anterior papillary muscle. In the left ventricle the knife was inserted through the outer wall on the left side, near the ventricular base. The cutting edge was directed toward the septum, the anterior cusp of the mitral valve cut and then a slit made on the upper portion of the septum just below and parallel to the base of the aortic valve. If the electrocardiogram taken after the initial attempt showed no change from the normal (as was frequently the case), the knife was reinserted through the ventricular wall and another cut made.

In the case of the indirect or auricular route, a brass cannula was inserted into the ventricle by way of the auricle and the auricular appendage tied around it.

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Then the knife was introduced into the ventricle through the cannula, the bore of which fitted the knife handle. In the right ventricle the knife was directed into the ventricular cavity until it nearly touched the junction of the anterior wall and septum at a point just below the pulmonary cusps. It was then withdrawn with the cutting edge against the septum and a slit made so as to transect the main branch also in its course to the anterior papillary muscle. In the left ventricle the cutting edge of the knife was directed toward the upper portion of the septum, and after transection of the anterior cusp of the mitral valve, a slit was made on the septal wall just below and parallel to the base of the aortic cusps.

Following the initial attempt, the blade of the knife was withdrawn into the lumen of the cannula and an electrocardiogram taken. If the latter showed no change from the control, the operation was repeated. After the desired lesion was produced, tracings were taken at frequent intervals over a prolonged period of time to demonstrate the permanency of the change. Although both methods yielded satisfactory results, the auricular route seemed to be preferable for the left ventricle and the ventricular route for the right.

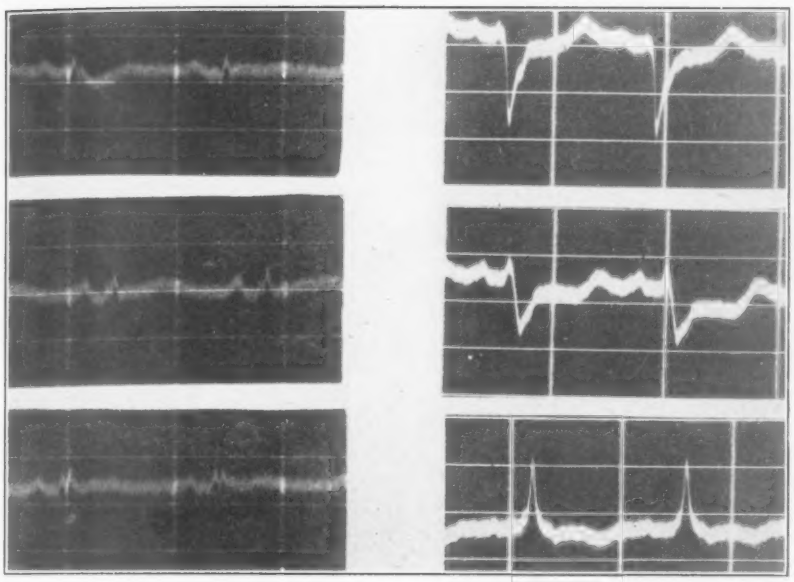
All specimens were examined postmortem and the cuts verified. The main right branch is readily seen as a grayish-white strand in its course to the anterior papillary muscle,[7] and if the slit transected the branch, it was obvious to the naked eye without having to resort to microscopic investigation. The main left branch is not so visible but is identifiable below the junction of the right and posterior aortic cusps. A slit parallel to the cusps and just below them usually transected the main branch before its division into its sub-branches.

RESULTS

Twelve successful experiments were performed, in six of which the right division of the bundle of His was cut and in the remaining six the left. Other experiments were done in which varying degrees of trauma were seen on the opposite side of the septum to the ventricle into which the knife had been introduced. All these, even those in which this damage was minimal, were ruled out with one exception. In that case (cat 15) complete heart-block was produced in addition to left bundle-branch block. However, as there was no evidence of damage to the right ventricle in the region of the right division but only to the main bundle at a higher level, it seemed justifiable to include this experiment in the series. It may be mentioned that in all the discarded experiments in which no considerable damage was done to the opposite side of the septum, the results supported those described below.

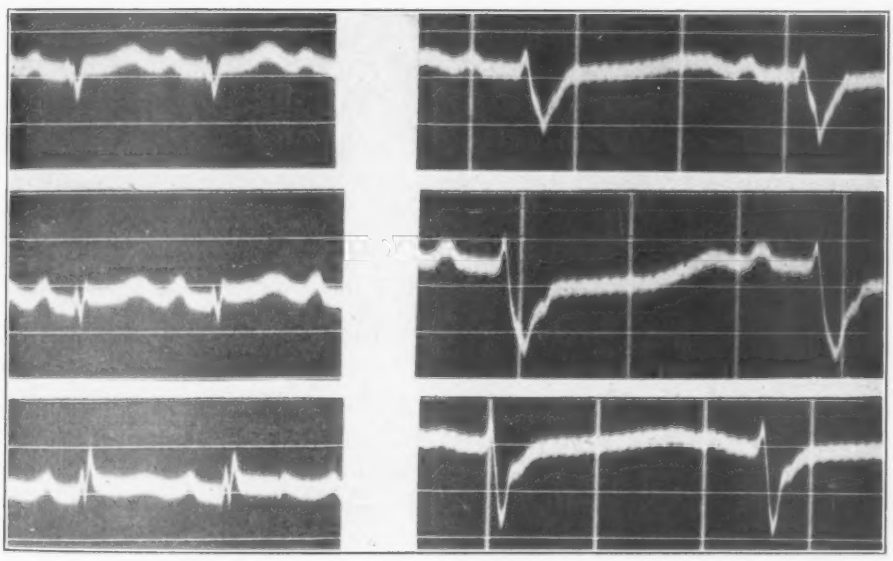
Control electrocardiograms taken after the introduction of the knife into the ventricle before transection of the division showed no significant change from the normal. Even in those cases in which post-mortem examination revealed some deep as well as superficial cuts, none of which had transected either of the main branches, but all of which had caused considerable damage to the endocardium and myocardium of the septum, no gross change in the form of the electrocardiogram was produced. This latter observation has been previously made by Eppinger and Rothberger[8] in their work on the hearts of dogs.

Typical electrocardiograms of both the discordant and the concordant type, using these terms in the same sense as they were employed by



A B

Fig. 1.—*A*, Normal. *B*, Right division cut. Discordant type. Time, one-fifth second. 1 cm. = 1 millivolt.



A B

Fig. 2.—*A*, Normal. *B*, Right division cut. Concordant type.

TABLE I

	NORMAL									RIGHT BRANCH OF BUNDLE OF HIS CUT										
	LEAD I			LEAD II			LEAD III			LEAD I			LEAD II			LEAD III				
CAT. NO.	R.	S.	T.	R.	S.	T.	R.	S.	T.	R.	S.	T.	R.	S.	T.	R.	S.	T.	TYPE	REMARKS
1	0	2	+1	0	4	+3	2	3	+1.5	0	7	+1.5	1	8.5	+2.5	5	1	+1	discordant	
6	1	0	0	2	0	+0.5	1.5	0	0	0	9	+2	1	6	+2	6	0	–5	discordant	
9	0	3	+1	0.5	1.5	+1	3	0	+0.5	1.5	6.5	0	2	10	+1	2	9	0	concordant	
10	4	1	–3	2	0	+1	5	0	–1	0	6	+4	1	3.5	+3	6.5	1	–0.5	discordant	
17	3	0	0	5	0	+2	5.5	3	+1.5	1.5	5	+2.5	–	–	–	6.5	1	–1.5	discordant	
19	5	0	–2.5	6	0	–1	4	0.5	0	1	4	+0.5	3	7	+1.5	3.5	2	+0.5	concordant (?)	main broadening in "S" in all leads

Amplitude expressed in 0.1 millivolts.

Lewis, are illustrated. Tables have been constructed of the successful experiments in which the amplitude (expressed in one-tenth millivolts) of the main deflections in the control electrocardiograms are compared with those obtained after cutting one of the divisions of the bundle.

In order to avoid repetition it can be stated that all curves taken after the transection of a division showed a marked widening of the QRS complex.

Right Division Cut (Table I. Figs. 1 and 2).—In these experiments a very high grade of bundle-branch block, in many cases complete, was obtained in every instance. In four (cats 1, 6, 10, 17) the curves were discordant and in two (cats 9, 19) concordant.

Lead I. In each case the chief initial deflection was the S-wave. In three no R-wave was present, while in the other three R was of small amplitude. In five experiments T was positive, i.e., opposite to the chief initial deflection, while in the remaining one it was iso-electric.

Lead II. In every instance the chief initial deflection was the S-wave, while T was positive. The curves thus resembled those in Lead I.

Lead III. In four experiments the chief initial deflection was R. In these S was practically absent. In one (cat 9) the chief deflection was S, which made the curves concordant. This was the only instance in which S was higher in Lead III than in Lead I. In another (cat 19) R was slightly larger than S, but the time interval of S was much greater than R; hence it seemed that those curves should also be considered concordant. T was of low voltage in every case. In three it was slightly negative, i.e., opposite to the chief deflection, in two slightly positive, and in the remaining one isoelectric.

Left Division Cut (Table II. Figs. 3 and 4).—In three experiments a complete block of the division was produced while in the others the block was of high grade. In one instance auricular fibrillation took place during the experiment, which of course did not affect the ventricle except as to rate and rhythm. Two experiments gave markedly discordant curves (cats 15, 16), two slightly discordant (cats 3, 14), while the other two were slightly concordant (cats 4, 11).

Lead I. In every instance the chief deflection was R. In no experiment was S present, while T was always negative, i.e., opposite to the chief deflection.

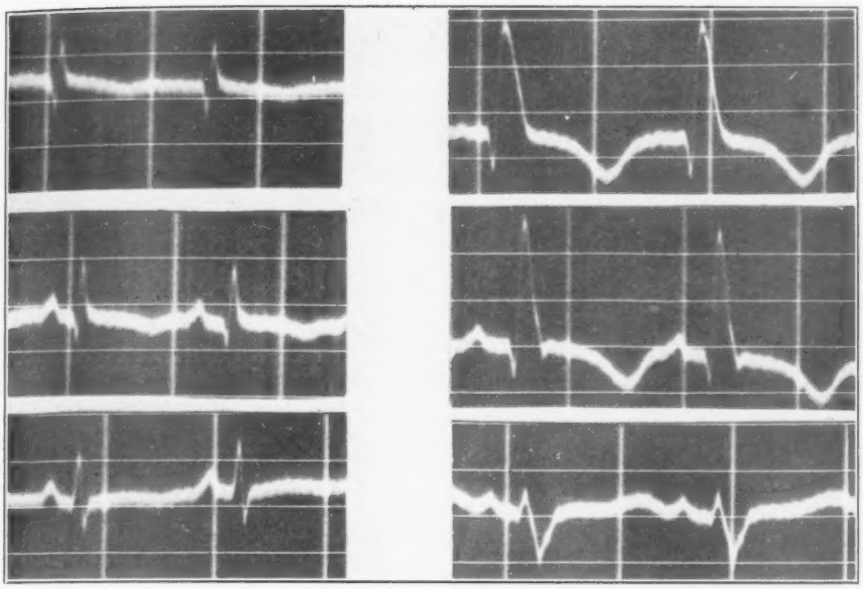
Lead II. In all the experiments the chief initial deflection was R. In none was S seen, while T was negative except in one case. The curves resembled those in Lead I.

Lead III. In four experiments the chief initial deflection was S. In two of these (cats 15, 16) R was almost absent, while in the other two (cats 3, 14) a definite R was seen, although its voltage was less than S. In another instance (cat 4) R and S were equal, while in the remaining one (cat 11) R was slightly greater than S. In the latter the normal curve showed an R of very low voltage in Lead I while in Lead III its amplitude was high, with S absent in both leads, i.e., some right axis

TABLE II

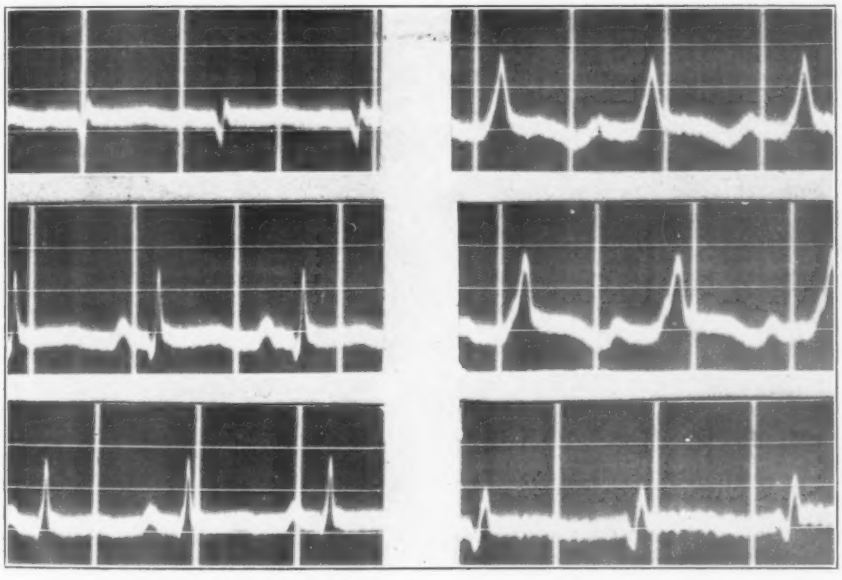
	NORMAL									LEFT BRANCH OF BUNDLE OF HIS CUT										
	LEAD I			LEAD II			LEAD III			LEAD I			LEAD II			LEAD III				
CAT. NO.	R.	S.	T.	R.	S.	T.	R.	S.	T.	R.	S.	T.	R.	S.	T.	R.	S.	T.	TYPE	REMARKS
3	1.2	0	–0.8	4	0	–2	2.5	3	0	13.5	0	–3.5	12	0	–2.5	3	5.1	–1	slightly discordant	
4	2	0	0	3	0	0	0.5	0	0	6	0	–2	8.5	0	0	2.5	2.5	0	concordant (?)	
11	1	0	0	6.5	0	+2	5	0	+1	4.5	0	–2	7	0	–3	4	3	–2	slightly concordant	
14	5	0	+1.5	6	0	+0.5	1.5	0	0	8	0	–6	7.5	0	–4	2	3	0	slightly discordant	auricular fibrillation
15	2	0	0	1	4.5	0	2	5.5	+1	6	0	–2	2.5	0	–3.5	1	4	+0.5	discordant	complete heart block
16	6	0	–2	6	0	–0.5	5.5	3	0	9.5	0	–3.5	13.5	0	–5	1.5	5	+1.5	discordant	

Amplitude expressed in 0.1 millivolts.



A B

Fig. 3.—*A*, Normal. *B*, Left division cut. Discordant type.



A B

Fig. 4.—*A*, Normal. *B*, Left division cut. Concordant type.

deviation. This was the only case in which the normal curves showed a much greater amplitude of R in Lead III than in Lead I. In none of the concordant tracings was the amplitude of R in Lead III as great as that in Lead I. In two experiments T was slightly positive, in two slightly negative and in the other two iso-electric.

DISCUSSION

The interpretation of the initial phases of human bundle-branch block curves advanced by Lewis is based upon anatomical consideration and the order of ventricular activation as determined in the dog and assumed to be similar in the human. Wilson[6] and Mann[5] have both pointed out that the conclusions derived from experiments on the canine heart should not be so applied without taking into consideration the marked differences between canine and human hearts in regard to the position of the anatomical axes and the angle of the interventricular septa. Wilson has criticized Lewis' analysis of the discordant levocardiograms obtained by the latter in a small percentage of dogs because surface readings were taken from hearts in which the form of the levocardiogram was not investigated and compared with the electrical axis calculated from a discordant levocardiogram, a type known to be exceptional in the dog. Furthermore, the position of the canine heart with respect to the three standard leads varies from that of the human, and there is also a material difference in the distribution of the sub-branches of the right division of the bundle. Large and important strands of conduction tissue which bridge the cavity of the dog's right ventricle are not found in man.

Barker and his collaborators,[4] given an extraordinary opportunity to study the excitatory process in an exposed human heart, stimulated various points on the surface of the two ventricles and simultaneously recorded the three standard leads. All the curves obtained from the right ventricle showed upward chief initial deflections in Lead I, while all those from the left ventricle were in the opposite direction. They further found that as the superior aspect of the heart was approached Leads II and III tended to become inverted, indicating that the form of the electrocardiogram of a ventricular extrasystole is dependent upon both the Purkinje system, right or left, to which it first spreads, and the level at which it enters the system. Available evidence indicates clearly that the form of a right ventricular extrasystole resembles the curve of left bundle-branch block and vice versa. Their concordant curves (chief deflections all in the same direction) supported the conclusions arrived at by Lewis with regard to bundle-branch block, but their discordant curves (chief deflections opposite in Leads I and III) were in complete disagreement with his findings. Our results in the cat agree with those of Barker and his coworkers. Whether the curves obtained were discordant or concordant, division of the right main branch resulted in the

chief deflection in Lead I being downward, while after division of the left branch the chief deflection in Lead I was upward.

Wilson and Herrmann[9] in their experiments on dogs obtained only concordant curves and the majority of Lewis' tracings were also of this type. When all of these are analyzed, it is found that in Lead I the chief initial deflection was downwardly directed when the right division was cut, and in the opposite direction on transection of the left division. Our results differed from these in that at least half of the curves were of the discordant type. However, when Lead I alone was considered, they were grossly similar to the above. It is a significant fact that in all of our curves, both concordant and discordant, the deflections which were most definitely of the type resembling those seen in humans were found in Lead I. Any deflections which did not correspond exactly to human curves (possibly due to a small part of the division not having been cut) were present in Lead III. Even in our concordant curves, except in one instance, the chief deflection was always less in Lead III than in Lead I, revealing a tendency toward the discordant type. Thus it seems that in deciding on the division which has been affected Lead I is the important lead to study.

Since we have no evidence at present to indicate that the architecture of the junctional tissue, the interventricular septal angle, the position of the heart relative to the standard limb leads or other anatomical factors in the cat more closely resemble the human arrangement than in the dog, we realize that our results cannot be considered completely decisive with regard to the interpretation of human curves.

SUMMARY

1. Experiments were performed on cats in which either the right or left division of the bundle of His was cut.

2. Both concordant and discordant curves were obtained. On transecting the right division, the chief initial deflection in Lead I was downward in both types, but in Lead III it was upward in the discordant type and the reverse in the concordant. On cutting the left division exactly opposite results were found.

3. In analyzing the curves, the important lead to study in order to decide upon the location of the lesion appeared to be Lead I.

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AN ANALYSIS OF THE QRS COMPLEX OF THE ELECTROCARDIOGRAM*

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CONSIDERABLE evidence has accumulated which indicates that the electrocardiogram, previously interpreted as showing right bundle-branch block, probably is associated with a disturbance of conduction in the left bundle branch. This has cast some doubt upon the applicability of Einthoven's mathematical principles to the abnormal ventricular complexes. It is the purpose of this analysis to demonstrate their applicability as well as their value in understanding the form of the complexes observed in ventricular preponderance, bundle-branch block, and ventricular extrasystoles.

There are certain limitations that must be borne in mind in using Einthoven's method for the study of electrocardiograms. The conditions necessary for calculating the electrical axis by means of the equilateral triangle are approached only when the electrodes are situated in radially different directions and at a sufficient distance from the heart so that all points in the vicinity of each electrode are practically equipotential. (From the standpoint of potential distribution in a fluid-conducting medium, each electrode may then be considered at an almost infinite distance and therefore equidistant from the source.) Wilson and Herrmann[1, 2] have shown that beyond 15 inches from the heart, there is very little potential difference between any two points along the same radial line. Accordingly, this method may be applied to records obtained from the usual limb electrodes but not to records taken with chest electrodes which are less than 15 inches from the center of the heart. With limb electrodes, only the potential differences generated along the frontal plane of the three electrodes are recorded in the standard leads. Consequently, any part of the heart which generates potential differences perpendicular to this plane does not influence the electrocardiogram.

It is well known that the equilateral triangle and the electrical axes calculated from it are merely a schematic approximation of the electrical phenomena actually present in the heart and surrounding tissues. This was stressed by Einthoven[3] who noted, however, that there was sufficient correspondence for practical purposes. Slight variations in the inclination of the axis cannot therefore be used for estimating changes in the direction of the electrical current produced in the heart.

The wave of excitation probably consists of an advancing doublet of positive charges immediately followed by negative charges. This has

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recently been confirmed experimentally by Craib[4] who also disproved the mass theory which hypothesized that relative negativity alone was developed during the excitatory process. Accordingly, the electrical energy generated by an individual muscle fiber is a consequence of the potential difference created by this doublet. The electrical axis at any particular interval represents the direction and is proportional to the magnitude of a potential difference which is the resultant of an algebraic summation of all the individual potential differences produced by activation in the heart at that time. The axis therefore indicates the predominant direction of activation which usually corresponds to the direction of activation in that sector of the heart generating the greatest potential differences at that moment. Craib stated that there could be no quantitative relation between the voltage of the electrocardiogram and the weight of the myocardium in the sense that one is directly proportional to the other. This follows if an increase in weight of the muscle mass is so proportioned that the increments of the various sectors balance each other. If, however, the increase in weight is localized to a sector in which the excitation wave courses in the same general direction, the voltage is affected. When the fibers transmitting the excitation wave longitudinally are thicker in such a sector, the potential differences generated there become proportionately greater and the resultant electrocardiogram is influenced by this alteration.* If the excitation path is lengthened by increase in length of the individual fibers, the potential differences last for a longer period and consequently alter the electrocardiogram.

In this analysis, the main part of the QRS deflection is considered. The initial part of the QRS complex has been dealt with in another article (Fenichel and Kugell[6]). For purposes of comparison, the axis calculated at the time of the maximum deflections in the three leads is used, as this best represents excitation in the major mass of ventricular musculature. Sometimes the maximum peaks in the three leads do not occur simultaneously but at slightly different intervals. Since all the axes during the period of the maximum deflections usually lie in the same direction, a similar significance may be attached to any one of them.

VENTRICULAR PREPONDERANCE

Fig. 1 contains the successive electrical axes of the QRS complexes from a normal electrocardiogram. In constructing the diagram, Lewis'[5] measurements and calculations were used. Each standard lead was taken simultaneously with a direct chest lead so that the precise time

* The following formula: $V = \frac{Q}{2\pi kd} \log_e \left(\frac{R_1}{R_2}\right)$ governs the distribution of potential in a thin homogeneous conducting sheet. V is the potential at any point distant R_1 and R_2, respectively, from the two poles; Q is the quantity of electricity flowing in unit time; k is the coefficient of conductivity of the medium; d is the thickness of the sheet.

V is in direct proportion to Q which depends upon the number and thickness of the individual fibers provided they lie in the same direction. Hence the potential difference registered between any two electrodes in the surrounding conducting medium is directly proportional to the mass of these fibers.

relations were known. At 0.0400 sec. the maximum deflections occur in all three leads. The electrical axis at this time is at 55° and is directed downward and to the left.

Fig. 2 is plotted from Lewis' electrocardiogram of left ventricular preponderance which was obtained from a case of chronic nephritis with marked left ventricular hypertrophy. The most prominent initial ventricular deflection is upward in Lead I and downward in Lead III. The

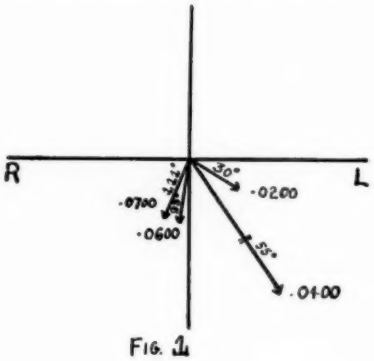

FIG. 1

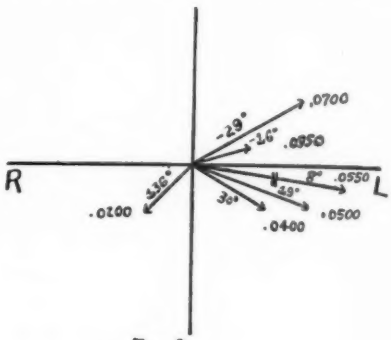

FIG. 2

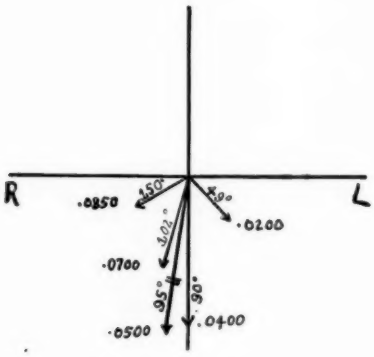

FIG. 3.

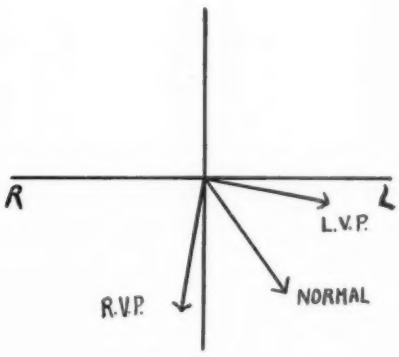

FIG. 4.

Fig. 1.—The electrical axes of successive intervals during the QRS deflections of a normal electrocardiogram. Measurements and calculations from Lewis.[5] The measurements at 0.0400 sec., the time of the maximum deflections, are 6, 11, and 5 for Leads I, II, and III, respectively (in one-fifth millivolts). The length of each axis is drawn somewhat proportional to the manifest potential difference. The axis at the time of maximum deflection is designated by the transverse parallel lines.

Fig. 2.—The axes of a left ventricular preponderance record. From Lewis. Values at time of maximum deflection are 11, 7, and -4.

Fig. 3.—The axes of a right ventricular preponderance record. From Lewis. Values at time of maximum deflection are -1, 9.5, and 10.5.

Fig. 4.—Comparison of the electrical axes of maximum deflection from the previous three figures.

maximum deflection occurs at 0.0550 sec. and the electrical axis is at 8°, pointing almost directly toward the left. During successive intervals, a gradual upward rotation of the electrical axes is evident. This is probably due to the influence of the upward inclining potential differences from the later activated basal portions.

Fig. 3 presents the axes from Lewis' record of right ventricular preponderance observed in a case of mitral stenosis with marked right ventricular hypertrophy. The principal initial deflection is downward in Lead I and upward in Lead III. Here, the maximum of the initial deflection is at 0.0500 sec. and its electrical axis is at 95°, downward and slightly to the right.

In Fig. 4 are contrasted the electrical axes at the time of maximum deflection for the three cases given above. The axis for the left ventricular preponderance has rotated to the left of the normal position, while the axis for the right ventricular preponderance has rotated to the right. The rotation of the axis in either case is probably due to the electrical predominance of the wall of the hypertrophied chamber, where potential differences of greater magnitude and longer duration are produced by the activation of the widened and elongated muscle fibers.

The QRS interval in an electrocardiogram showing left ventricular preponderance is often found to be widened to as much as 0.12 sec. This is probably dependent upon the additional time necessary for activating the thicker walls of the hypertrophied chamber. The alteration in the conduction system as a result of dilatation of the chamber may also be a factor in the delay.

For general usage in the interpretation of electrocardiograms, the term axis deviation is preferable to ventricular preponderance, since records resembling those of the latter are obtained from normal individuals without any evidence of ventricular hypertrophy. In such instances, the axis deviation is probably due to the variation in anatomical relations of the ventricles. Left axis deviation records are often observed in sthenic individuals with broad horizontal hearts, while right axis deviation records are seen in asthenic indivduals with long vertical hearts.

BUNDLE-BRANCH BLOCKS IN DOGS

In the normal electrocardiogram of a dog Wilson and Herrmann[7] observed a QRS interval of 0.043 sec. On cutting the right bundle branch in this dog the interval was increased to 0.067 sec. The difference of 0.024 sec. may then be regarded as the time lost in the aberrant course of the excitation wave traveling through the septum from the left side to the right Purkinje network. These observers then recorded normal ventricular complexes from the same animal by means of properly timed stimuli to the conus region of the right ventricle. A delay of 0.03 seconds or more in the stimulation of the right ventricle resulted in complexes of right bundle-branch block, while less delay yielded complexes which were transitional between normal and right bundle-branch block. It is therefore evident that during the registration of the right bundle-branch complexes, diffuse muscular excitation in the right ventricle began about

0.03 sec. later than in the left ventricle. Moreover, since the normal activation of both ventricles required only 0.043 sec., electrical activity in the intact left ventricle was practically completed at 0.04 sec. and entirely over at 0.05 sec., at which periods the maximum deflections of the aberrant complexes were recorded. Thus it is seen that the maximum deflections of the right bundle-branch complexes represented principally the potential differences of the delayed right ventricular activation which was no longer opposed by the normal left ventricular activation.

The initial ventricular deflections are observed to be higher after section of either bundle branch. This is probably an effect of the unneutralized potential differences produced by the ventricle with the damaged bundle branch. There is no basis for assuming the alternative, that a larger total of potential differences is generated by such a heart. In the transitional complexes of less width, mentioned above, the deflections are not as prominent, since there is less disturbance of the normal balance.

On cutting the right bundle branch in dogs, Lewis, and also Wilson and Herrmann,[7] rather consistently obtained concordant records with the most pronounced part of the initial ventricular deflection negative in the three leads. Wilson and Herrmann later cut the remaining left branch and secured electrocardiograms of complete heart-block. Both observers autopsied all hearts and confirmed the site of the right bundle-branch incision, so that the accuracy of their work can hardly be questioned. On two occasions when the right bundle branch was clamped, Lewis obtained definitely discordant records with upward initial ventricular deflections in Lead I. In analyzing the levocardiogram, he utilized the latter records which can hardly be considered ideal for experimental deductions, since the preoperative electrocardiograms showed unusually high R-waves in Lead I.

Fig. 5 is plotted from one of Lewis' concordant electrocardiograms with principal deflections downward in all three leads, recorded after section of the right bundle branch. In the tabulation, Lewis presented the measurements for only part of the QRS interval, to 0.0550 sec. After this time, at which the peaks occur in the three leads, the complexes return to the iso-electric line without ever becoming positive. Therefore, all the electrical axes at later intervals are in the same quadrant, upward and to the right. Hence, the actual values beyond 0.0550 sec. are not necessary for this analysis.

Until about 0.0250 sec., the axis is principally directed downward and to the left (at 0.0200 sec. when the early deflections are most prominent). Probably this is due to activation in the intact left ventricle which, to some extent, is balanced by simultaneous septal excitation. After this, the principal deflection appears, and with it there occurs an abrupt rotation of the electrical axis. At 0.0550 sec., the time of

maximum amplitude, the axis points upward and to the right, indicating prevailing activation in the wall of the right ventricle. This is in accordance with the conclusion already noted: that the maximum amplitude of the aberrant complex represents the unbalanced activation in the delayed chamber. In the dog, the right ventricle lies above as

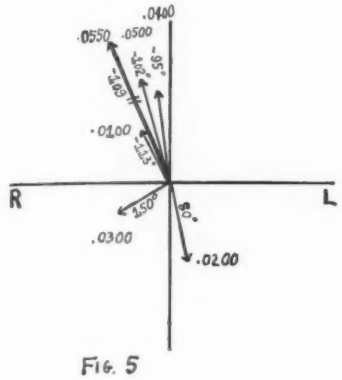

Fig. 5

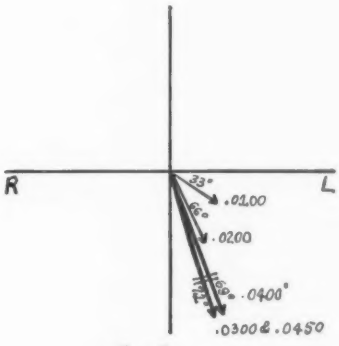

Fig. 6

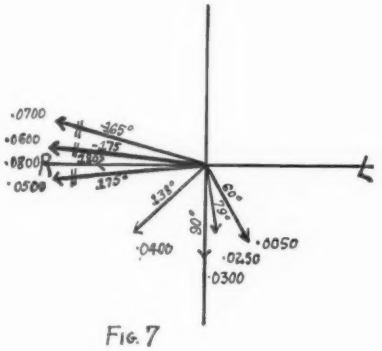

Fig. 7

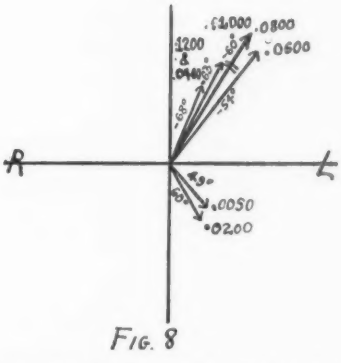

Fig. 8

Fig. 5.—The axes of a record obtained after severing the right bundle-branch in the dog's heart. From Lewis. Values at time of maximum deflection at -5, -15, and -10 (in one-tenth millivolts).

Fig. 6.—The axes of a record following incision of the left bundle-branch in the dog's heart. From Lewis. Values at time of maximum deflection are 4.5, 12.5, and 8.

Fig. 7.—The axes from an electrocardiogram of the infrequent type of bundle-branch block in man. From Lewis. Values at time of maximum deflection are -12.5, -7.5, and 5.

Fig. 8.—The axes from an electrocardiogram of the common type of bundle-branch block (Fig. 10). From a case at Montefiore Hospital. At autopsy, the heart showed marked fibrosis of the entire left side of the interventricular septum. The deflections at successive intervals were measured with a comparator. The values at time of maximum deflection are 11, -11, and -22.

well as to the right of the other ventricle, and its basilar region has more mass than its apical region which rests on the interventricular septum. Thus, the right ventricle in situ resembles an inverted cone. This may account for the marked upward inclination of the axis at the time of maximum deflection, for its direction suggests relative preponderance of the base of that chamber.

The initial ventricular complexes obtained by Lewis, and by Wilson and Herrmann, after cutting the left bundle branch in the dog, are also concordant with the main deflection upward in the three leads. Fig. 6 is charted from one of Lewis' records. Here all the axes are directed downward and to the left. At 0.0400-0.0450 sec., the time of maximum deflection, the preponderant direction of activation is accordingly downward and to the left. Since the dog's left ventricle simulates an upright cone, the direction of these axes can be correlated with the main line of excitation in the left chamber. During the early intervals, the axis is not directed to the right. Septal activation, occurring simultaneously with excitation in the comparatively thin right ventricular musculature, probably overcomes any such tendency.

On inspecting the above two analyses, it is seen that the axis at the time of maximum deflection points in the direction of the chamber

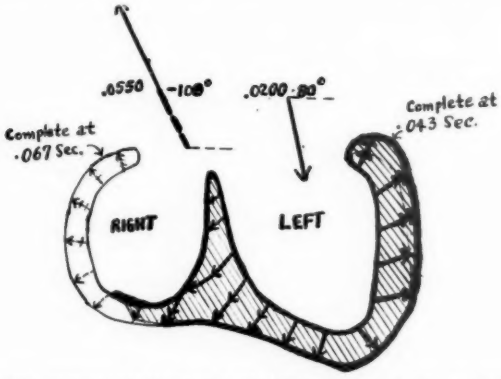

Fig. 9.—Schematic representation of activation in the dog's ventricles after cutting the right bundle-branch. The shaded part indicates the area activated before or at 0.03 sec. The axis at 0.02 sec. conforms to the predominant direction of earlier activation in the left ventricle. The axis at 0.055 sec. corresponds to the predominant direction of later activation in the right ventricle.

whose bundle-branch conduction is impaired, thus representing the activation in the outer wall of that chamber. Moreover, the dextrocardiogram of Lewis (the ventricular complexes observed after severing the left branch) is a representation of activation in the intact right ventricle for approximately only the first third of the QRS interval; and the main part of the complex, which occurs after this, essentially represents the unopposed activation in the wall of the left ventricle. Similar conclusions follow in regard to the levocardiogram. Algebraic summation of the dextrocardiogram and levocardiogram gives a complex resembling the normal complex for only the first third of their intervals or for over half of the normal QRS interval. During this time, the potential differences of relatively normal activation of the right ventricle are added to those of the left ventricle. The slight difference observed between the calculated and the normal complexes is due to the abnormal septal activation. Probably, in bundle-branch block the entire septal wall is activated from the intact side, while in

the normal heart each half of the septum is activated from its own side. To some extent, the potential differences arising from the unidirectional, and consequently slightly prolonged activation of the muscular septum neutralize those resulting from simultaneous activation in the wall of the intact ventricle. This may account for the low voltages recorded during the first third of the QRS interval in records of bundle-branch block.

Lewis recorded the time of arrival of the excitation wave over the surface of the right ventricle in a dog with right bundle-branch block. At 0.0294 sec. after the beginning of the initial ventricular deflection in the simultaneous axial lead, the region of the right ventricle just lateral to the interventricular groove showed activity. The levocardiogram at 0.0400-0.0550 sec. cannot therefore be considered as representing only left ventricular excitation when there is direct evidence that a part of the right chamber is activated before this time. Fig. 9 is a schematic representation of activation at 0.0300 sec. in the dog's ventricles following severance of the right bundle-branch.

BUNDLE-BRANCH BLOCK IN MAN

Before analyzing human electrocardiograms of bundle-branch block, note should be made of some of the essential differences between the human and the canine heart. The left ventricle in man lies posterior to and to the left of the right ventricle. Since the three ordinary leads record only potential differences along the frontal plane, the two ventricles can be regarded as lying lateral to each other. In the frontal plane of the dog, on the other hand, the right ventricle lies above as well as to the right of the other chamber. The QRS interval of the normal complex in man lasts from 0.05 sec. to 0.08 sec., while in bundle-branch block this interval is prolonged from 0.12 sec. to 0.16 sec. As in the dog, the time delay is probably due to the later activation of the ventricle, homolateral to the bundle-branch block. These figures are about double the corresponding measurements in the dog, the human heart being larger and its musculature thicker. Complexes which are transitional between normal and bundle-branch block are also seen in man, and the QRS intervals are accordingly intermediate in duration. Hence, the interpretation of electrocardiograms with left axis deviation, inverted T-wave in Lead I, and normal QRS interval (less than 0.11 sec. which is observed in ventricular preponderance alone) as incomplete bundle-branch block by Luten and Grove[8] is unwarranted. A normal QRS interval infers simultaneous activation in both chambers.

Fig. 8 is drawn from the measurements of an electrocardiogram (Fig. 10), taken at Montefiore Hospital, showing the common type of bundle-branch block with principal initial ventricular deflection upward in Lead I and downward in Lead III. These curves were not taken simultaneously with a chest lead but were moved until $e_1 + e_3 = e_2$. At

autopsy the heart of this patient showed marked fibrosis of the entire left side of the septum. The right side of the septum was intact. At 0.0800 sec., the time of the maximum deflection, the electrical axis points upward and to the left. The axis at maximum deflection in a similar record reported by Lewis, was inclined directly toward the left (5°). Since at 0.0800 sec. the normal QRS complex would be either completed or at least beyond the maximum deflection, the excitation in the intact ventricle at this time may be considered almost at an end. Accordingly, at the time of maximum potential, the axis indicates the unbalanced activation of the delayed ventricle. From its

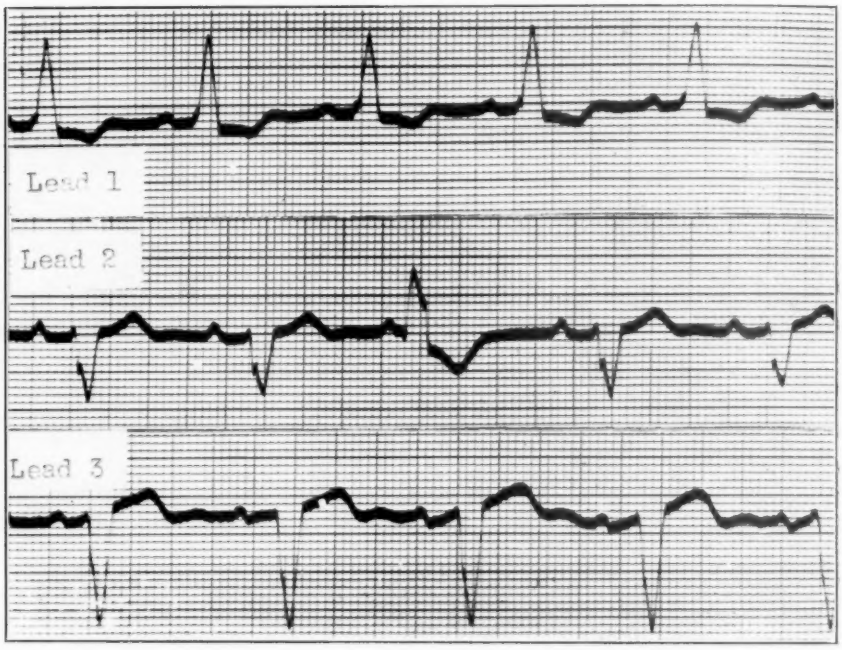

Fig. 10.—The common type of bundle-branch block. QRS interval 0.14 sec. In Lead II, there is a left ventricular extrasystole appearing immediately after the P-wave. This may be explained by the onset of an independent left ventricular excitation process which follows a short time after the normal onset of excitation in the sino-auricular node.

left direction, it can represent only predominant activation in the wall of the left ventricle, and, therefore, the electrocardiogram in question should be interpreted as left bundle-branch block. As in the dog, the axis of maximum deflection points in the direction of the chamber whose bundle branch is blocked. The counterclockwise rotation of the successive axes may be explained by the later activation of the basilar portion of the left ventricle where the excitation wave has an upward inclination.

In his interpretation of a similar electrocardiogram, Lewis considered the axes at early intervals as representing septal activation, and

at later intervals (0.0700 sec.) as representing lateral wall excitation in the intact left ventricle. Therefore, the complex was termed a levocardiogram due to right bundle-branch block. But at 0.0700 sec., as well as until the end of the QRS interval, the axes are still directed to the left. His analysis revealed no evidence of a subsequent activity in the right ventricle, and, therefore, his levocardiogram represented an isolated contraction of the left ventricle. The interpretation presented here explains the activation of both chambers and corresponds to the experimental work in dogs. In 1920 Fahr,[9] from considerations based upon the theory of mass negativity during activation, interpreted the type of record under consideration as left bundle-branch block.

Fig. 7 is plotted from Lewis' electrocardiogram of the less common type of bundle-branch block with principal deflection downward in Lead I and upward in Lead III. At 0.0500-0.0700 sec. the greatest amplitudes occur, and the axes are pointed almost directly toward the right. Their time and direction indicate a later unbalanced right ventricular excitation, and the electrocardiogram should be interpreted as right bundle-branch block. The axis at the time of maximum deflection thus points toward the chamber whose bundle-branch conduction is impaired. In the early intervals, the direction of the axis is probably the result of predominance of left ventricular excitation over aberrant septal activation.

The principal phases of the QRS complexes in the three leads are essentially the same in right bundle-branch block and right ventricular preponderance, since the principal deflections of the former are due to the unopposed potential differences of the retarded right chamber, while in the latter they result from the predominant potential differences of the hypertrophied right chamber. A corresponding similarity is present in regard to left bundle-branch block and left ventricular preponderance. A combination of the two conditions in the same chamber accordingly produces deflections of even greater voltage. The common type of bundle-branch block occurs frequently in patients with hypertension and left ventricular hypertrophy. Hence the complexes are often higher than those of right bundle-branch block records, where concomitant right ventricular hypertrophy is infrequent. Bundle-branch block is differentiated by its wider and notched QRS complexes which are opposite in phase to the T-waves in all three leads. Presumably, the notching is caused by the irregular generation of potential differences on account of delayed activation in one ventricle (Wilson and Herrmann[7]). Displacement of the heart to the left also amplifies the principal deflections of left bundle-branch block. Combinations of right or left bundle-branch block with ventricular preponderance or heart displacement can thus produce many atypical and confusing records with a wide QRS interval. In addition, considerable

pleural or pericardial fluid may reduce the voltage and so distort the record (Oppenheimer and Mann[10]).

FUNCTIONAL INTRAVENTRICULAR CONDUCTION DISTURBANCES

Electrocardiograms of bundle-branch block are most frequently seen in cases of coronary artery disease with degenerative changes and fibrosis in the myocardium. A functional impairment in conduction is probably a contributory factor in some cases where no organic lesion is demonstrable in either bundle-branch. With the rapid ventricular rate accompanying auricular fibrillation, the electrocardiogram frequently exhibits such impairment in conduction.

Wolff, Parkinson and White[11] recently reported eleven records of bundle-branch block obtained from healthy young individuals without any evidence of heart disease. The P-R intervals in their tracings are unusually short (often less than 0.1 sec.), so that the wide QRS complexes immediately follow the P-waves without any intervening iso-electric period. Normal complexes preceded by normal P-R intervals were often recorded in this series after release of vagal tone by exercise or atropinization. In the electrocardiogram of one case manifesting an abrupt change from the normal to the abnormal complex, the P-S intervals of both are found to be equal. This means that there is no additional time taken for the entire excitation process from its onset in the sino-auricular node to its completion in the ventricles. Hence, it is suggested that the mechanism is a functional bundle-branch lead rather than block. For some unexplained reason, perhaps vagal influence, there is no retardation at the auriculoventricular node of the auricular impulse to one bundle branch, while the other branch receives its impulse after the normal delay. A left bundle-branch lead would then give ventricular deflections identical with those of right bundle-branch block. Another possibility is that there is present in one ventricle a secondary center which under the influence of the extracardiac nerves stimulates that ventricle at a fixed time after the onset of the sino-auricular impulse. It is interesting to note that Wilson and Herrmann have obtained similar records in dogs on stimulating the right ventricle after cutting the right bundle branch. In one of their records where the direct excitation of the right ventricle preceded the intact left supraventricular activation by 0.031 sec., the wide QRS complexes of complete left bundle-branch block followed immediately after the P-wave. The left ventricular extrasystole in Fig. 10 also resembles the unusual complexes seen in Wolff, Parkinson and White's records.

VENTRICULAR EXTRASYSTOLES IN DOGS

It is well known that the complexes of ventricular extrasystoles are similar to those of bundle-branch block. On direct stimulation of either

ventricle, the excitation wave travels through the muscular wall to the endocardium where it spreads rapidly throughout the entire ventricle by means of the Purkinje network. Lewis has shown that a small preliminary deflection results from the passage of the wave through the thick muscular wall, and that the more prominent QRS wave begins with the onset of widespread ventricular activation. The aberrant course of the excitation wave to the second ventricle, probably through the septum, results in retarded and unbalanced activation in that chamber. The resemblance of the complexes of right ventricular extrasystoles and left bundle-branch block can thus be understood.

In 1913, Rothberger and Winterberg[12] studied the form of the complexes obtained on direct electrical stimulation of the dog's ventricles at various points. The electrodes of Lead I were connected to the forelegs. The electrodes of Lead II were placed in a vertical line, one electrode being inserted into the esophagus and the other into the anus. These observers were primarily interested in the form of the ventricular complexes and so did not carefully standardize their electrocardiograms. The normal as well as the extrasystolic complexes were recorded in both leads.

On scrutinizing their recorded extrasystolic complexes, it is seen that the electrical axes of the principal deflections are directed toward the later activated ventricle. A complex with the principal deflection upward in Lead I was obtained upon stimulation at all points on the right ventricle. The positive deflection indicates that all the axes at the time of maximum amplitude point toward the left (Lead I represents the horizontal vector of the electrical axis). On stimulation of the surface of the left ventricle, a complex with a negative principal deflection in Lead I was obtained at all points but three, which are located at the apex near the interventricular sulcus. Thus, all left ventricular axes except those calculated from points on the apex are directed toward the right.

The initial ventricular deflections from the three points at the apex of the left ventricle are found to be of almost normal width when the preliminary deflections, due to the initial passage of the excitation wave through the thick muscle wall, are not included. By direct electrical stimulation at the apex of the left ventricle, Lewis obtained similar intermediate complexes for some distance to the left of the interventricular sulcus. Such complexes also resemble the transitional type which Wilson and Herrmann produced by slightly delayed stimulation of the ventricle with a severed bundle branch. In each instance the type of complex is dependent upon almost simultaneous activation in both ventricles. Accordingly, it can be seen why the axes of the complexes obtained at the apex by Rothberger and Winterberg approximate the normal axis which is directed toward the left (in the dog, the main deflection of the normal QRS complex in Lead I is upward).

Upon stimulation at the left apex, more rapid conduction along the longer path to the right Purkinje network may account for the approximately simultaneous activation of the two ventricles. In his observations on the course of the excitation wave in the auricles, Lewis found the conduction rate to be 1252 mm. per second along the interauricular band, whereas it was only 588 mm. per second near the superior vena cava. This difference in rate, he attributed to the oblique direction of the fibers along the latter path. Therefore, it may be assumed that muscle fibers conduct the excitation wave more rapidly along their long axes. On section of the heart, Lewis observed that the muscle fibers at the left apex coursed laterally toward the right ventricle. Hence, the more rapid conduction of the excitation wave to the right ventricle is prob-

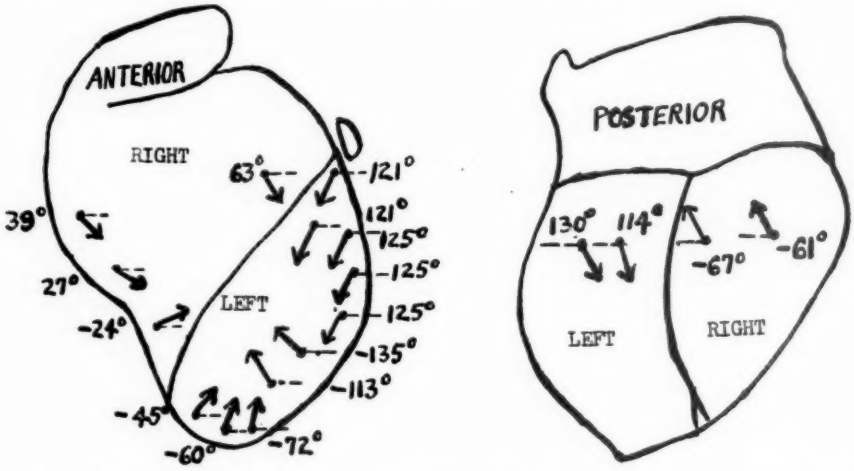

Fig. 11.—Diagrams of the anterior and posterior surfaces of the dog's ventricles with Rothberger and Winterberg's points of stimulation. The axis charted at each point is calculated from the abnormal QRS complexes which they obtained upon stimulation at that point.

ably due to transmission along the length of the fibers, while conduction to the left ventricle occurs across the fibers.

In the experiments of Rothberger and Winterberg, Lead I is practically at right angles to Lead II, and since they represent respectively, the horizontal and vertical projections of the electrical axis, the latter can be calculated. In view of the fact that the ratio of the maximum amplitudes of the normal complexes in both leads is fairly constant, standardization for comparative study is possible. This has been accomplished by correcting the values of the maximum deflections of the extrasystolic complexes in proportion to a fixed ratio of the normal complexes. Because of the use of four different dogs and the presence of overshooting in several records, some margin of error is to be expected. The error is found to be relatively slight in comparison with the marked variation in the complexes recorded at the different points of stimulation.

Diagrams are presented of the anterior and posterior surfaces of the

dog's heart with the points of stimulation (Fig. 11). The axes charted at these points are calculated from the maximum deflections of the abnormal complexes in their records. As noted above, the axes of all points on the surface of the right ventricle point toward the left. Except for the apical region, all left ventricular points show a deviation of their axes toward the right. A regular rotation of the electrical axes is seen from cephalic to caudal points. The axes of the former have a downward direction while those of the latter incline upward. The explanation of the right or left direction is presented in the discussion of bundle-branch block. The rotation of the axes between superior and inferior points of the same ventricle is considered later.

EXTRASYSTOLES PRODUCED IN MAN

Barker, Macleod, and Alexander[13] recently obtained electrocardiograms following direct electrical stimulation of the human heart. The subject had streptococcus pericarditis for which the pericardial sac was widely opened after the resection of several ribs. The lower portion of the ventricles being thus exposed, the relations of the points of stimulation could be determined fairly accurately. The ventricular complexes which they obtained resemble those of ventricular extrasystoles and bundle-branch block seen in clinical electrocardiograms. The main initial ventricular deflection is upward in Lead I for all points on the surface of the right ventricle, and downward for all points on the surface of the left ventricle. Hence, the principal deflections in Lead I are in the same phase as those of bundle-branch block of the opposite chamber. A preliminary deflection due to the passage of the excitation wave through the muscle wall is also seen in the complexes from points on the left ventricle.

In Fig. 12 are charted the electrical axes of maximum deflection at the points of origin. Any inaccuracy in measuring the maximum deflections in their records is almost negligible in comparison with the marked variations of the complexes at the different points of stimulation. The axes of all right ventricular points are directed toward the left, while the opposite holds true for points on the surface of the left ventricle. In each instance, the axis is directed toward the later excited chamber.

Barker et al observed prominent variations of the main deflections in Leads II and III between cephalic and caudal points of the same ventricle (points 10, 7, 6, 4). At point 10, the main deflections were upward in Lead II and Lead III, while at point 4 they were downward in the two leads. Since the main deflections in Lead I were upward at both points, the complexes of point 10 were concordant and those of point 4 discordant. They suggested that this probably resulted from the altered order in which various portions of the ventricles became active.

An analysis of the electrical axes yields an explanation for these variations in the complexes. On observing the electrical axes in Fig. 12, a

regular rotation is evident at points along a vertical line. The axes of the superior points of each chamber have a downward direction while those of inferior points have an upward direction. The same observation is noted in the forced ventricular contractions produced by Rothberger and Winterberg in the dog's heart (Fig. 11). During normal activation in either ventricle, the many divisions of the bundle branch distribute the excitation wave rapidly over the entire Purkinje network so that the various regions differ only slightly in the time of arrival of the excitation wave (in proportion to their distance from the bundle branch, the

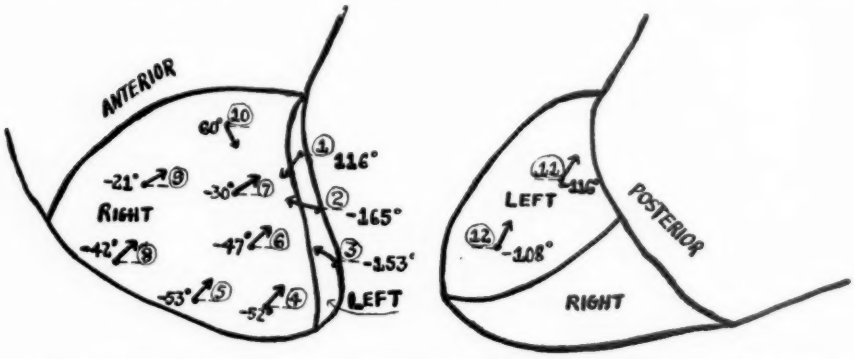

Fig. 12.—Diagrams of the lower anterior and posterior surfaces of the human ventricles showing Barker, Macleod, and Alexander's points of stimulation with the axes calculated from the recorded complexes.

basilar regions receiving the wave somewhat later). When, however, either ventricle is stimulated at a cephalic point, the underlying Purkinje network transmits the excitation wave to the superior half of that ventricle first. Since the lower portion of this ventricle is activated later, part of its excitation remains to oppose the delayed excitation in the other ventricle. Consequently, the downward directed potential differences generated by the lower portion of the first ventricle divert the electrical axis of maximum deflection, resulting essentially from activation in the wall of the second ventricle, somewhat downward. In a similar manner, upon stimulation at a caudal point, the upward inclined potential differences generated in the later excited superior portion of the first ventricle elevate the axis of maximum deflection. Furthermore, the axis of an intermediate point approximates that of a bundle-branch block of the opposite chamber. The axis at point 7 is 30° upward and to the left, whereas the axis of maximum deflection in the record of left bundle-branch block in man, presented above, is 60° upward and to the left. The axis of point 2 is 15° upward and to the right, while the axis in the record of right bundle-branch block is 5° upward and to the right.

In clinical electrocardiograms, it is possible that the exact origin of a ventricular extrasystole may be ascertained after calculating its axis of maximum potential and comparing it with those charted in Fig. 12. In

the experiments of Barker et al, the outer surface of the ventricle was stimulated, whereas ventricular premature beats are thought to arise from foci in the Purkinje tissue. This difference in the origin of the impulse may alter the time at which various regions of the ventricle are activated, so that comparison is not fully justifiable. In addition, other conditions, such as preponderance in one ventricle or position of the heart, affect the direction of any axis and offset calculations. Nevertheless, it is reasonably certain that a premature ventricular contraction originates in the right ventricle, if its main QRS deflection is upward in Lead I, while a main downward deflection in Lead I signifies left ventricular origin.

Wilson, Macleod, and Barker[14] recently demonstrated the inadequacy of Lewis' interpretation of the particular side involved in either type of bundle-branch block and presented a nomenclature similar to the one in this paper. However, in applying the principles of excitation deduced from the hypothetical shell of muscle to the excitatory process in the ventricles, Wilson and his associates disregarded some of Lewis' well-established observations. During normal ventricular activation, they assumed that the entire endocardium as well as the adjacent muscle tissue becomes activated almost simultaneously. Accordingly, the direction of the electrical axis becomes essentially an inverse function of the ventricular breaks or openings where no opposing electromotive force exists. Yet there is sufficient evidence to indicate that the various endocardial regions are not activated simultaneously and that the entire QRS interval is not required for excitation of the muscle walls alone. Lewis and Rothschild's endocardial readings show a very rapid, almost simultaneous, activation in the dog's right ventricle, but this may be due to the special bridge of conducting tissue which extends across the chamber. The endocardial readings in the left ventricle were not considered very reliable because of the disturbing influence of the strong muscular contractions. Nevertheless, the epicardial readings of both ventricles point to a later activation of the bases that cannot be accounted for solely by the thickness of the underlying muscle wall. Although conductivity in the specialized conducting tissue is five to ten times more rapid than in the ordinary myocardium, the path through the former is at least five to ten times longer than that through the thickest part of the ventricular wall. It is therefore more reasonable to infer that the time necessary for the impulse to reach any point of the endocardium is directly proportional to the distance from its bundle branch and that the activation of the nearer muscular regions dominates the early QRS deflections. Hence a correlation of the electrical axis with the particular regions probably activated at that time appears to be a more direct and less complex method of analyzing the excitatory process than the method in which a correlation with the ventricular openings is sought. In accordance with Lewis' concept, the QRS interval can readily be divided into an early

period, approximately the first third representing excitation principally in the septum and adjacent inferior portions of both ventricles, and a later period containing the maximum deflection and representing lateral wall and basal excitation. A division into shorter periods is impracticable because of considerable overlapping in the time of activation of different sectors.

The form of the canine electrocardiogram is definitely altered by cutting the anterior or posterior division of the left bundle branch while the QRS interval remains unaffected. This would favor the view that a disturbance of the normal order of activation has occurred in that chamber, i.e., the activation of the region previously supplied by the incised division becomes somewhat delayed, although its excitation still occurs before the process is completed at the base. It is difficult to account for such an alteration merely by a modification in the tangential components which may be accurately applicable to the hypothetical shell of muscle but not to the heart, where several distorting factors are present. While the tangential components dominate the electrical effects produced by the endocardial network, the voltage from this source is too small to be recorded in the electrocardiogram. Even with a complete reversal of the direction of the excitation wave in the endocardial network, the influence of the tangential components upon the path in the muscle tissue is quite small, inclining the line of excitation only 11° to 23° from the normal line (2a where tan a = 1/10 to 1/5). Moreover any tendency of varying tangential components to divert the excitation wave from the usual path is offset by the fixed postion of the individual muscle fibers in relation to the endocardial network from which the impulse is received, and by the constant conduction of the excitation wave along the length of the individual fibers, since longitudinal transmission is probably more rapid.

Wilson, Macleod, and Barker maintained that the prominent deflections of the QRS complexes in bundle-branch block are primarily due to the aberrant activation of the entire septum from the intact side, and they therefore stressed the importance of the position of the septum. But we have sufficient data available to believe that the septum is activated fairly early, and this appears likely since the septum is nearest to the intact bundle branch. Subsequent to severance of the right bundle branch, right ventricular activity just beyond the intraventricular groove was detected at 0.0294 sec. by Lewis and Rothschild whereas the maximum deflection of the abnormal complex usually occurs later (about 0.04-0.055 sec. in the dog). Wilson and his coworkers' statement that the later and major part of the canine dextrocardiogram may be attributed to the electrical effects of activation of the septum and right apical region is open to the criticism that time relations were not considered, for Lewis and Rothschild showed that in the intact heart the outer surface of the right apex usually becomes active at 0.0120 sec.

According to Wilson, Macleod, and Barker, the major deflections recorded in hypertrophy of one ventricle may be a consequence of the augmented electrical effects of the opposite half of the hypertrophied septum. Although the septum is hypertrophied, the effects of activation entering from one side tend to neutralize those of simultaneous activation from the other side. The concept advanced in this paper is similar to their alternative view, that the axis deviation may be due to increased electrical effects from the wall of the hypertrophied ventricle. The preliminary deflections in ventricular preponderance are correlated with septal position in a previous communication (Fenichel and Kugell). There is at present no basis for assuming that they are sequential to some delayed activation in the hypertrophied chamber.

SUMMARY

1. In ventricular preponderance, the deviation of the electrical axis is probably an effect of the greater potential differences generated by the wall of the more hypertrophied ventricle.

2. The principal initial ventricular deflections of bundle-branch block represent the unopposed potential differences of delayed activation in the wall of the ventricle with impaired conduction.

3. The principal deflections of ventricular extrasystoles result from the unopposed potential differences of delayed activation in the ventricle, contralateral to the one from which the excitation impulse arises.

Note at time of correction of proof: The recent experimental studies of bundle-branch block in the cat by Roberts, Crawford, Abramson and Cardwell[15] are also contrary to the former interpretation of bundle-branch block. In Lead I they obtained a negative principal deflection after incision of the right bundle branch and a positive principal deflection after incision of the left bundle branch.

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Department of Clinical Reports

CHANGES IN THE ELECTROCARDIOGRAM IN THE COURSE OF PERICARDIAL EFFUSION WITH PARACENTESIS AND PERICARDIOTOMY*†

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ELECTROCARDIOGRAMS obtained soon after coronary occlusion have so regularly shown the R- or S-T segments originating on the terminal limb of R or S before the latter reaches the iso-electric level, that such findings have been considered almost pathognomonic of acute coronary closure.

In the experimental animal such R- or S-T abnormalities have been observed after coronary ligation,[1, 2] after injection of toxic material into the muscle of the ventricle,[3] after a toxic dose of digitalis,[4] after injection of fluid into the pericardium,[5] and during induced general anoxemia.[6]

That such "plateau type" R-T segements may occur in clinical conditions other than coronary occlusion was first shown by Scott, Feil and Katz,[7] who in 1929 reported this finding in a case of aneurism ruptured into the pericardium and in a case of purulent pericardial effusion. In neither instance was coronary disease found at autopsy. These authors attributed the electrocardiographic changes to increased hydrostatic pressure in the pericardial sac which, in their opinion, caused anoxemia of the heart muscle. Shearer,[8] and later Master and his associates[9] reported the occurrence of this abnormality of the electrocardiogram in the course of lobar pneumonia with a subsequent return to normal in the patients who recovered.

We have had the opportunity to observe a patient with pneumococcic pericarditis with effusion, in the course of which paracentesis and later pericardiotomy were done, in whom daily electrocardiograms showed the "plateau type" of the R-T segment returning to normal in the presence of severe toxemia, progressing to death on the twenty-first day. No coronary disease nor gross myocardial damage was found at autopsy.

CASE REPORT

A white male, aged thirty-five years, was admitted on December 26, 1930, in severe shock complaining of pain in the left side of the chest and of prostration. He had been under our observation for two weeks with cough and fever ranging from 99° to 103° F. Physical signs during this time were negative except for inflammation

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of the upper air passages. This seemed to be subsiding until the day before admission when he was suddenly seized with intense pain in the precordia that required morphine for relief. On admission there was shock, with rapid shallow respiration and also marked cyanosis. The blood pressure could not be satisfactorily determined. The left border of the heart was about 12 cm. from mid-sternum, no arrhythmia was present and no murmurs or pericardial frictions were heard. Dullness was present over the left lung base, and a harsh pleural friction was heard in the precordial area. After a roentgenogram had showed the heart shadow greatly enlarged, a diag-

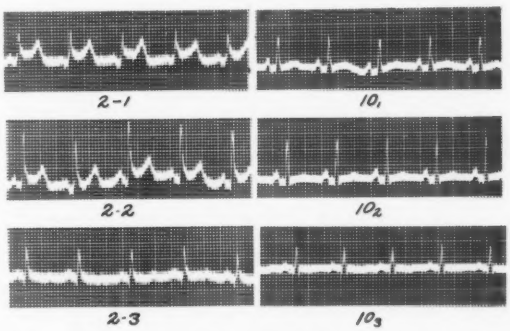

Fig. 1.—(Left) Record taken on the third day of illness showing elevation of the R-T segment in first and second lead. (Right) Record taken on eleventh day of illness showing normal R-T segments.

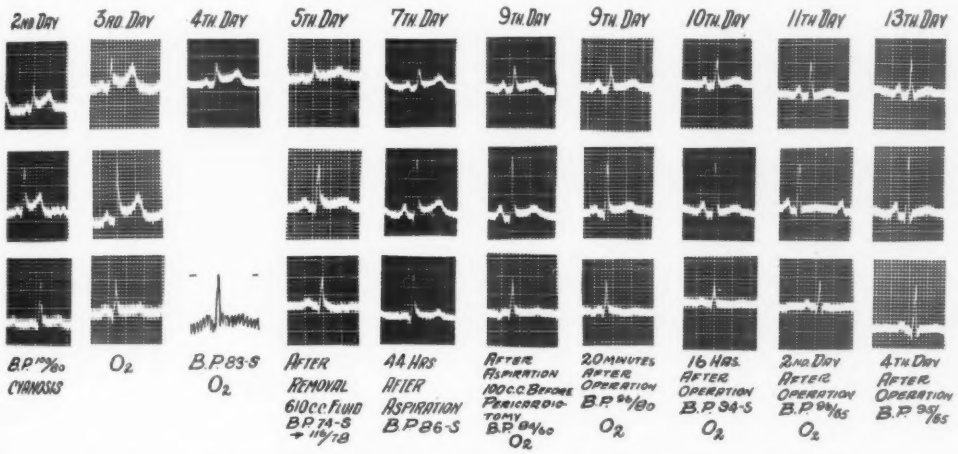

Fig. 2.—Single complexes from the three leads of records obtained during the clinical course. These with the clinical notes below each record show the lack of change during the administration of oxygen, and the gradual return to normal following removal of fluid.

nosis of acute pericarditis with effusion was made. On the following day a to-and-fro friction was heard over the precordia. The first electrocardiogram, which was made on December 27, suggested that we might be dealing with coronary occlusion rather than with pericardial effusion, and the original diagnosis might have been relinquished but for the physical signs and roentgenograms typical of pericardial effusion and for the observations of Scott, Feil and Katz previously referred to. On account of marked cyanosis, anoxemia was presumed to be considerable and oxygen was administered continuously at the rate of 5 to 6 liters per minute. This was followed by definite decrease in the cyanosis, though the character of the electrocardiogram was unaltered.

The blood pressure showed a progressive fall; on December 27, 100 systolic, 80 diastolic; on December 29, 83 systolic and on December 30, 74 systolic. Paracentesis was done on December 30, and 610 c.c. of slightly turbid fluid were removed. Following paracentesis the blood pressure rose to 116 systolic and 78 diastolic. On January 3, 1931, 100 c.c. of pus were aspirated and pericardiotomy was advised and was done on the same day.

At operation about 150 c.c. of pus under slight pressure were evacuated. Oxygen, which had been discontinued following the paracentesis, was readministered. Transfusions of 250 to 300 c.c. of blood were given on January 6, 8, and 10 in an effort to combat the toxemia, which seemed the dominant factor in the illness. Later, when blood cultures showed a growth of Pneumococcus Type I, antipneumococcic serum (Felton) was given. Death occurred on January 15, 1931, apparently from toxemia which had progressed steadily from the onset.

DISCUSSION

Changes in the R-T segment of the electrocardiogram such as are present in this case have been attributed to a number of factors among which are: (a) injury to the ventricular muscle, (b) toxemia, (c) general anoxemia, and (d) anoxemia of the heart muscle. In the case here reported three of these conditions were present and must be considered as possible factors.

Toxemia, to which such changes in the electrocardiogram occurring in pneumonia, have been attributed by Master and his associates,[9] was present and progressive, and in our opinion was the cause of death. It is interesting to note that the infection was caused by the Pneumococcus Type I. Since normal electrocardiograms were obtained at a time when the toxemia was the dominant feature of the illness, we believe that it was not a considerable factor in this case.

In considering the rôle of general anoxemia, we have no determinations of the oxygen content of the blood, but have assumed that the presence of marked cyanosis and rapid shallow respirations, which were relieved following the administration of oxygen, was indicative that anoxemia was present to a considerable degree. The electrocardiograms taken while oxygen was being given were similar in every respect to the ones obtained previously, so that it seems fair to conclude that general anoxemia was not the dominant factor in the production of the electrocardiographic changes.

The first change toward normal in the electrocardiogram was noted in the record taken immediately after removal of 610 c.c. of fluid by paracentesis on December 30 and consisted of slight but definite lowering of the R-T segment and diminished amplitude of the T-wave. It may be assumed that the hydrostatic pressure within the pericardium continued to be less after this paracentesis, since only 100 c.c. of pus were obtained by aspiration on January 3 and only 150 c.c. found on pericardiotomy on the same day. This fall in pressure was paralleled by gradual return of the electrocardiogram to normal, which point was reached on January 5.

These clinical observations together with daily electrocardiograms seem to us to confirm the conclusions of Scott, Feil and Katz, that the electrocardiographic abnormalities resulted from local anoxemia of the heart muscle arising from the tamponade effect of increased hydrostatic pressure within the pericardium.

CONCLUSIONS

We believe that increased hydrostatic pressure within the pericardium, diminishing both venous return and coronary flow, resulting in anoxemia of the heart muscle, was the dominant factor in the electrocardiographic abnormalities in this case.

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Department of Reviews and Abstracts

Selected Abstracts

Lichtman, S. S.: Isolated Congenital Dextrocardia. Report of Two Cases With Unusual Electrocardiographic Findings: Anatomic, Clinical, Roentgenologic and Electrocardiographic Studies of the Cases Reported in the Literature. Arch. Int. Med. **48:** 683, 1931.

Isolated dextrocardia is defined in its strictest sense as a primary independent dextroposition of the heart. In this article a clinical analysis of the symptoms, signs, roentgenographic and electrocardiographic evidence and diagnostic features is attempted, based on a study of one hundred and sixty-one cases of isolated dextrocardia reported in the literature.

Etiologic, pathogenic and anatomic considerations are reviewed. A comprehensive classification inclusive of known and possible anatomic variations is presented.

Two personal cases are presented with unusual electrocardiographic findings, the result of associated congenital cardiac malformations and their effects.

Carter, Edward P., and McEachern, Donald: Recurrent Complete Heart Block. Report of a Case Associated With Transient Bundle-Branch Block and Normal Conduction Between Attacks. Bull. Johns Hopkins Hosp. **49:** 337, 1931.

The patient whose illness is reported illustrated a number of unusual and interesting points with regard to the cardiac mechanism and its reaction to various drugs. Briefly these were: (1) recurrent complete auricloventricular dissociation (and Adams-Stokes seizures) with normal conduction between attacks; (2) paroxysmal bundle-branch block; (3) an idioventricular rhythm, during the periods of complete auriculoventricular dissociation, which arose sometimes on the left side and sometimes on the right; (4) the development of ventricular tachycardia following an overdose of epinephrine intravenously; (5) the onset of status anginosus during thyroid therapy.

The details of these observations are reported together with a possible explanation for their occurrence.

MacCallum, W. G., and Taylor, J. Spottiswood: The Typical Position of Myocardial Scars Following Coronary Obstruction. Bull Johns Hopkins Hosp. **49:** 356, 1931.

The importance of recognizing the scarred area in the heart following obstruction of a coronary artery slowly produced by arteriosclerosis and often completed by thrombus formation is pointed out. There is a gradual wasting of the cardiac muscle in the affected area somewhat smaller than that ordinarily supplied by the obstructed artery with replacement by fibrous tissue.

Three typical photographs from a long series of specimens are reproduced to show the contrast between the effect of obstruction of the anterior descending branch of the left coronary artery, of its left circumflex branch and of the right coronary artery.

Weinstein, Alfred A., and Weiss, Soma: The Significance of the Potassium-Calcium Ratio and of the Inorganic Phosphorus and Cholesterol of the Blood Serum in Arterial Hypertension. Arch. Int. Med. **48**: 478, 1931.

A study of the significance of the potassium calcium ratio and the inorganic phosphorus and cholesterol of the blood serum in seventy-five cases of hypertension and twenty-five control cases is presented. This investigation was undertaken to determine whether or not changes could be demonstrated in the level of the potassium calcium and cholesterol of the blood tested by the reliable methods available and when the patients were selected after a detailed investigation of the clinical state. Since the calcium level of the blood varies inversely with the inorganic phosphorus level, determinations of the inorganic phosphorus were also performed.

The average potassium level rose from 20 to 22.15 mg. per hundred cubic centimeters of serum in seventy-five cases of hypertension with or without secondary complications. This rise was most marked in cases of hypertension with cardiac involvement in which the average level was 22.8 mg. per hundred cubic centimeters. The average calcium level in these cases was normal (9.75 mg. per hundred cubic centimeters) as compared with that of the control group (9.8 mg. per hundred cubic centimeters).

The correctness of the observations on the normal amount of calcium in arterial hypertension was supported by the fact that the inorganic phosphorus level in these cases (4.1 mg. per hundred cubic centimeters) showed no tendency to increase above the average amount of inorganic phosphorus in the controls (4.3 mg. per cent) while the calcium inorganic phosphorus ratio of the seventy-five cases of hypertension (2.43) showed no tendency to fall below that of the control cases (2.33). The potassium calcium ratio rose from a control level of 2.05 in twenty-five cases to 2.32 in seventy-five cases of hypertension with or without involvement. This rise was most marked in patients with hypertension and cardiac involvement (2.38) and least in patients with uninvolved hypertension (2.19). The slight increase observed in the cases of hypertension was probably due to the impairment of the circulatory functions.

The cholesterol level rose from a control level of 171.6 to 204.5 mg. per hundred cubic centimeters in seventy-five cases of hypertension with or without involvements. This was most marked in patients with hypertension and renal involvement (227 mg. per hundred cubic centimeters) and least in patients with hypertension and cardiac involvement (194 mg. per hundred cubic centimeters). Of thirty-seven cases of uninvolved hypertension, only five (13 mg. per hundred cubic centimeters) showed an unexplainable hypercholesteremia. There was no relation between the potassium ratio and the cholesterol content of the blood in hypertension.

Neither changes in the potassium calcium ratio nor changes in hypercholesteremia can be considered as playing a fundamental rôle in the development of arterial hypertension. Elevation of the potassium and cholesterol levels observed in one group of patients with hypertension is the result rather than the cause of changes in the cardiovascular system in arterial hypertension.

Harrison, T. R., Turley, F. C., Jones, Edgar, and Calhoun, J. Alfred: Congestive Heart Failure. X. The Measurement of Ventilation as a Test of Cardiac Function. Arch. Int. Med. **48**: 377, 1931.

A series of standard exercises has been described during and after which the ventilation was measured. The expression: $\frac{\text{ventilation}}{\text{vital capacity}} \times \frac{1 + \frac{\text{ideal weight}}{\text{actual weight}}}{2}$ has

been denoted as the ventilation index, and the values for this are relatively independent of the nutritional state. It is believed that the ventilation index affords a fairly accurate objective answer to the question of breathlessness.

From the data obtained during the study it is felt that dyspnea is directly proportional to the ventilation per square meter and inversely proportional to vital capacity. The degree of dyspnea is closely proportional to the expression: $\frac{\text{ventilation}}{\text{vital capacity}}$. It was found that the actual dyspnea was greater in obese subjects and often less in very thin subjects than in persons of normal nutritional status. It was also found that the index was usually normal in subjects with cardiac neurosis. The ventilation index was found to be usually slightly above normal in subjects with early organic cardiac disease and was very much above normal in patients who have or who have had congestive failure. The ventilation index was also increased in persons with diminished vital capacities from pulmonary disease, in subjects with hyperthyroidism and in patients with severe anemia. The test is useless and actually misleading in persons with respiratory obstruction.

The authors believe that the test will be of some value in measuring the effect of various therapeutic measures, such as the administration of digitalis in patients with different types of cardiac disease in various stages of development.

Priestley, James T., Markowitz, J., and Mann, Frank C.: The Tachycardia of Experimental Hyperthyroidism. Am. J. Physiol. **98**: 357, 1931.

A series of experiments was performed by which it was shown that the heart rate of perfused hearts of thyroxinized rabbits and the heart-lung preparation of thyroxinized dogs is considerably greater than normal. Similary, when the heart of a small dog is transplanted into the neck of a large dog by means of anastomosis of blood vessels, the administration of thyroxin evokes definite tachycardia of the transplanted heart. It appears that the tachycardia of experimental hyperthyroidism is not dependent on the central nervous system but on a peripheral mechanism.

Brams, W. A., and Katz, L. N.: Studies on the Overdistended Heart. I. Effects of Venesection. Am. J. Physiol. **98**: 556, 1931.

The effects of venesection on the nondistended and on the previously acutely, overdistended heart of the anesthetized dog were compared. The overdistention was brought about by transfusion of defibrinated blood, physiological saline, gum acacia solution or by a mixture of the former two. The analysis was based on a study of graphically recorded volume curves, on optically recorded synchronous pressure pulses from the two ventricles, and from the aorta and pulmonary artery, on the pressure levels in the systematic and pulmonary veins, and on the electrocardiogram recorded by the three standard indirect leads.

Venesection in the nondistended heart caused a reduction in stroke volume of the ventricles, a decrease in the maximum pressure and pressure excursion of the ventricles during systole and a fall in the pressure level in the aorta and pulmonary artery. These changes are in accord with previous work on the effect of hemorrhage. The changes were more marked in the left ventricle and aorta. The stability of the diastolic pressure in the pulmonary artery was striking.

The subsequent course of events, which was followed for twenty minutes, was variable. In some experiments there was a progressive decrease in the pressure and stroke volume; in others there was a tendency for the pressure and stroke volume to increase again; in a few there seemed to be a stabilization of the heart's activity at the new level.

Venesection produced a different set of events in the acutely overdistended heart. In many instances venesection led to a further drop in stroke volume of the ventricles, a further decline in the maximum pressure and the pressure excursion of the ventricles during systole, and a further fall in the pressure level and pulse pressure in the aorta and pulmonary artery. In every one of the experiments in which this initial depression of the heart's action was noted, a further progressive depression was observed in the following periods up to twenty minutes. No instance of a secondary augmentation of the pressure levels or excursions was noted, probably because of the escape of the fluid (whose osmotic pressure was low) from the blood stream. The changes were more marked in the left ventricle but, unlike the nondistended heart, venesection produced, as a rule, a greater drop in the diastolic pressure of the pulmonary artery than in the aorta.

In some experiments venesection overcame the depressing action of overdistention, leading to a temporary or lasting improvement, at least up to twenty minutes. This improvement was evidenced by an augmentation of the stroke volume, by an elevation of the maximum pressure and pressure excursion of the ventricles during systole or both, and by a rise in the systolic and pulse pressures in the aorta and pulmonary artery, occasionally accompanied by a rise in the diastolic pressure level and by a fall in the pressures in the systemic and pulmonary veins.

Venesection in the previously overdistended heart was always associated with a decrease in diastolic volume and in initial pressure, the drop in the latter being as a rule greater in the left ventricle. In the nondistended heart, bizarre variable changes were noted in the initial pressure, although the diastolic volume consistently dropped. These bizarre changes in initial pressure are ascribed to artefacts inherent in the experimental method which are sufficiently large to mask occasionally the true changes in the nondistended heart but not the larger changes in initial pressure following venesection in the overdistended heart.

The results reported indicate that venesection has a different dynamic effect on the acutely overdistended heart than on the nondistended one. In many instances an improvement in the dynamic action of the overdistended heart can be demonstrated; in others, however, the depression of the overdistended heart's pumping ability is apparently made progressively worse by venesection.

It is realized that the acutely overdistended heart in these experiments is not strictly comparable with the overdistended heart encountered clinically and that such factors as the presence of myocardial pathology and chronicity of the stasis and its effects, may alter the response to venesection. With these reservations, it is believed that considerable information has been gained in these experiments which may lead to a better evaluation of the clinical possibilities of venesection.

The changes in heart rate following venesection were variable in both the nondistended and the overdistended heart. The effect of these rate changes on the dynamics of the heart was evaluated in making the analysis of the results of venesection. Temporary or permanent slowing was as frequent a finding as acceleration. Slowing was usually but not always associated with a depression of the heart's dynamic action and with electrocardiographic evidence of intraventricular block or damage. The slowing in these cases was a sinus bradycardia. In extreme form it preceded the death of the animal. These observations suggest that a slowing up of the heart rate following venesection should be considered a sign of danger. The applicability of this test should be tried clinically.

An asynchrony in the pressure rise of the curves obtained from the two ventricles was observed as well as in the onset and end of the ejection period. Some changes in the asynchrony were noted as the condition of the heart altered. The straddle of the left ventricular pressure curve was found to be consistently longer than the right although the difference in the straddle of the two curves varied.

On the other hand, the duration of ejection was longer as a rule, on the right side, indicating that the periods of isometric contraction and relaxation were shorter in the right ventricle. The duration of ejection of the two ventricles decreased after venesection and increased on distention of the heart. No consistent changes in the duration of ejection were found when the heart was overdistended. The greatest abbreviation of ejection occurred in the moribund heart.

Katz, L. N., and Brams, W. A.: Studies on the Overdistended Heart. II. The Rôle of Relaxation in Filling the Distended and Overdistended Heart. Am. J. Physiol. **98:** 569, 1931.

In the course of these experiments a diastolic dip was seen resembling the one described in the isolated turtle heart by one of the authors when the heart was distended and overdistended. It was always observed in the right ventricular pressure curve and occasionally in the left. Its size in the right ventricular curve was a direct function of the diastolic size of the heart. The diastolic dip is not an instrumental artefact but expresses the pressure changes in the ventricle at this time. The dip is an exaggeration of the normal drop in the pressure present in the mammalian heart in the rapid filling phase and expresses an augmentation in the disparity between the rate of ventricular expansion and the rate of filling. An intraventricular pressure below atmospheric was never found in these experiments.

The diastolic dip indicates that ventricular relaxation plays a rôle in filling the mammalian heart by exerting an aspirating action during the rapid inflow phase.

Barrier, Charles W.: Tachycardia. Ann. Int. Med. **5:** 829, 1932.

Important features in a series of 26 cases of supraventricular tachycardia are noted. Cases of unusual duration are reported, one having an attack lasting three years, another being in a permanent attack for nearly six years unless treated.

Quinidine in most cases of supraventricular tachycardia is the more desirable drug for arresting an attack; though in the presence of heart failure digitalis will act and may be the drug of choice. In two cases where quinidine was continued for a year, it had to be used in increasing doses. Continuous digitalization has been extended for a period as long as one and a half years. While the continuous use of digitalis is to be preferred over quinidine, the drug must be used in such large doses that toxic effects appear.

Both digitalis and quinidine will slow the rate and arrest the attacks in the same patient. Until the mechanism of these attacks is better known, the mode of action of drugs cannot be explained. Digitalis did not arrest an attack in a patient who had received 1/15 grain of atropine. Both digitalis and quinidine act well by mouth and few cases need the drugs by vein.

Blackford, L. Minor, and Booth, William Telford: Dextrocardia Secondary to Eventration of the Diaphragm. J. A. M. A. **98:** 883, 1932.

A case of congenital dextroposition of the normal heart without evidence of transposition of other viscera secondary to eventration of the diaphragm in an athletic youth is reported.

The condition had been entirely asymptomatic up to the present, and it is believed that the position of the heart will never cause the patient any trouble. It is possible, however, that subphrenic symptoms may develop or that an extraordinary increase in intraabdominal pressure, brought on by trauma or tremendous exertion, may result in rupture of the weakened diaphragm.

Master, A. M., and Jaffe, Harry: Rheumatoid (Infectious) Arthritis and Acute Rheumatic Fever. The Differential Diagnosis. J. A. M. A. **98**: 881, 1932.

In 17 patients with rheumatoid (infectious) arthritis, on whom electrocardiograms were taken daily for an average of fifty-three days, only the slightest evidence of myocardial involvement was recorded. In 63 cases of acute rheumatic fever, however, definite electrocardiographic evidence of myocardial involvement appeared in 100 per cent. These electrocardiographic evidences of myocardial involvement have been sino-auricular block, nodal rhythm, interference of the sinus and auriculoventricular nodes, auricular fibrillation, auricular flutter, auriculoventricular (P-R) intervals of 0.21 second or more, heart block with dropped beats, definite R-S-T abnormalities, T-wave inversions and transient widening, notching and slurring of the QRS group. It is concluded from these studies that rheumatoid arthritis, no matter what it may be, is not especially a disease of the heart; acute rheumatic fever is preeminently a carditis.

If there is no electrocardiographic evidence of myocardial involvement in a patient with joint symptoms, it would be best to suspect rheumatoid arthritis; whereas, when there are electrical tracings definitely indicative of myocardial involvement, it is probably due to an acute rheumatic fever.

Barnes, Arlie R., and Ball, Ralph G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations. Am. J. M. Sc. **183**: 215, 1932.

In 1,000 unselected consecutive postmortem examinations more or less localized myocardial infarction was recognized grossly in 49 subjects. Of 685 of these subjects, forty years of age or more, myocardial infarction was observed in 47. The majority of the subjects who had sustained myocardial infarction had had associated hypertension as judged by the cardiac weights and the records of blood pressure.

Notable preponderance of arteriosclerosis in the left coronary artery over that found in the right was not observed in the hearts in which evidence of infarction was found. Gross myocardial infarction resulting from coronary occlusion was practically confined to the left ventricle. Myocardial infarction was observed in the posterior basal portion of the left ventricle in 24 instances as compared with 28 instances in which it involved the apex and anterior portion. More careful pathological study of the posterior basal portion of the left ventricle is urged in order that infarctions in that region be not overlooked.

In 28 instances infarction occurred in the region supplied by the anterior descending branch of the left coronary artery, as compared with 20 instances in which it occurred in the region of the left ventricle supplied by the right coronary artery. The designation of the anterior descending branch of the left coronary as "the artery of coronary occlusion" is no longer justifiable.

Ellis, Laurence B.: Studies in Complete Heart-Block: II. A Clinical Analysis of 43 cases. Am. J. M. Sc. **183**: 225, 1932.

An analysis is presented of 43 cases of complete auriculoventricular block in patients ranging in age from nine weeks to seventy-eight years. Seventy per cent of the patients were over forty years of age and the same percentage were males. In 29 cases the block was permanent, while in the remainder it was intermittent or temporary. Fifty-two per cent of the cases of permanent block were due to arteriosclerosis; 31 per cent were of undetermined origin but in most of these instances were probably either congenital or dependent upon on acute infection. Diphtheria, syphilis and rheumatic infection were responsible for a small number

of cases. Digitalis was the chief etiologic agent producing transitory block; although arteriosclerosis and infections caused a lesser proportion.

Complete heart-block per se may exist for very prolonged periods of time without damaging the health of the patient. Four cases are recorded in which the block is known to have existed for twenty-four, fifteen, fourteen and seven years respectively, and 2 more in which it has almost certainly lasted nine years. The chief factors governing the prognosis appear to be etiology, age, Adams-Stokes seizures, electrocardiographic abnormalities and cardiac size.

A discussion of the significance of arterial blood pressure findings is presented. Young persons with complete heart-block may have essentially normal blood pressures. A systolic arterial hypertension and wide pulse pressure usually occur in heart-block in persons giving evidence of peripheral arteriosclerosis.

Gouley, Benjamin A., and Eiman, John: The Pathology of Rheumatic Pneumonia. Am. J. M. Sc. **183**: 359, 1932.

Nine cases of acute rheumatic fever are presented with reference to their pulmonary pathology. Eight of these showed an acute inflammation of lung tissue with consolidation; the ninth showed pleurisy with subacute lung involvement. All of them were associated with acute rheumatic heart disease. The inflammatory pulmonary reaction consists of an interstitial perivascular exudate of large endothelioid cells, identical in morphology with those found in rheumatic heart lesions and considered pathognomonic of rheumatic fever. Hemorrhage and fibrinous exudate are prominent features. Eight of these cases exhibited pericarditis.

Wetherby, Macnider, and Clawson, B. J.: Chronic Arthritis With Special Reference to Intravenous Vaccine Therapy. Arch. Int. Med. **49**: 303, 1932.

Intravenous streptococcic vaccination brings about in patients two conditions (desensitization and a high agglutinating titer) that are regularly associated with the protection experimentally developed in animals against streptococci by intravenous vaccination. This analogous condition in vaccinated animals and patients affords a basis for intravenous vaccination in patients having chronic arthritis. Since subcutaneous injections of streptococci in animals tend to increase hypersensitiveness and only produce a low agglutinating titer in the serum, the subcutaneous method of vaccination in chronic arthritis would seem to be of less value than the intravenous method if not contraindicated. No ill effects have resulted from the intravenous vaccinations in the 100 cases studied. On the other hand, in 75 per cent of the cases the clinical improvement appears to be sufficient to justify the further use of this method of treatment for chronic arthritis.

Goldring, William, and Chasis, Herbert: Thiocyanate Therapy in Hypertension. I. Observations on Its Toxic Effects. Arch. Int. Med. **49**: 321, 1932.

Of the 50 patients with hypertension in this series treated 74 different times with thiocyanate, 13 presented toxic manifestations. In 11 of these the toxic manifestations disappeared within a few hours to four days after discontinuance of the drug. Two of these patients died as the result of thiocyanate poisoning.

The frequency and order of appearance of the various toxic manifestations are noted. A fall in the blood pressure, the occurrence of toxic manifestations and death were found to be unrelated to the amount of thiocyanate administered or to the amount of residual drug in the body. Data are presented showing that in some patients there is little or no margin of safety between the toxic and thera-

peutically effective dose of thiocyanate. Tissue analysis for thiocyanate and necropsy observations are presented in one of the fatal cases.

Schwartz, Sidney P.: Transient Ventricular Fibrillation. A Study of the Electrocardiograms Obtained From a Patient With Auriculoventricular Dissociation and Recurrent Syncopal Attacks. Arch. Int. Med. **49**: 282, 1932.

A study was made of the electrocardiograms of a patient with auriculoventricular dissociation who suffered from sixty-seven seizures of unconsciousness during a period of seven months. Each seizure was associated with periods of ventricular fibrillation. The longest recorded attack with spontaneous recovery lasted six minutes and two seconds.

The alterations in the electrocardiograms preceding a syncopal seizure consisted of a gradual acceleration through steplike progressions of both the basic auricular and the ventricular rates, the highest regular ventricular rate recorded being 65.2 beats per minute before ventricular fibrillation set in. Periods of reexcitation of from 4 to 11 beats at a time were observed to appear during the premonitory period, heralding the approach of a seizure of unconsciousness. The onset of every recorded seizure of ventricular fibrillation in this patient was initiated by a ventricular extrasystole which was always of the same character and arose from the same focus in the ventricle.

The ventricular rates during the periods of ventricular fibrillation varied from a minimum of 250 to a maximum of 1,000 beats per minute. Spontaneous revival usually coincided with the cessation of ventricular fibrillation. The mode of recovery was variable, but the restoration of the basic rhythm was preceded by an idioventricular rhythm, with a slightly irregular ventricular rate following, as a rule, a postundulatory pause.

Periods of unconsciousness in patients with auriculoventricular dissociation are associated with transient seizures of ventricular fibrillation much more commonly than has been suspected hitherto. A clinical diagnosis of transient ventricular fibrillation may be suspected in such patients if preceding a period of unconsciousness the heart rate has been noted to increase above that of the usual basic rate.

Dawson, Martin H., Olmstead, Miriam, and Boots, Ralph H.: Bacteriologic Investigations on the Blood, Synovial Fluid and Subcutaneous Nodules in Rheumatoid Arthritis. Arch. Int. Med. **49**: 173, 1932.

One hundred and five blood cultures, the majority in duplicate, were carried out on 80 patients suffering from rheumatoid arthritis according to the technic of Cecil, Nicholls and Stainsby. As control material, 31 samples of blood from normal persons and 16 samples of sterile autoclaved agar were subjected to similar manipulations. Blood cultures on patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance. No significant difference was observed in the bacteria encountered in the blood cultures of patients and those observed during the culture of the control material under similar conditions.

Streptococcus viridans was occasionally encountered during the culture of the control material as well as during the culture of specimens of the patients' blood.

Aerobic and anaerobic cultures of 23 specimens of synovial fluid obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance. Aerobic and anaerobic cultures of 12 subcutaneous nodules obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

Criep, Leo H.: The Effect of Bronchial Asthma on the Circulation. Arch. Int. Med. **49**: 241, 1932.

A complete cardiovascular survey of fifty patients suffering from bronchial asthma is presented. An electrocardiographic study of the acute asthmatic attack in eight patients is reported.

From these studies bronchial asthma apparently does not have a permanent damaging effect on the cardiovascular system. Acute attacks may as the result of the associated asphyxia produce minor transitory disturbances in cardiac conduction.

Schlesinger, Bernard: A Study of the Sleeping Pulse Rate in Rheumatic Children. Quart. J. Med. **1**: 67, 1932.

A study of the alert pulse rate is not sufficient to establish the presence of active carditis in afebrile children with rheumatic heart disease. Normally, the sleeping rate is on an average of ten beats per minute slower than the alert pulse.

A rapid alert pulse rate unaccompanied by a similar increase in the rate during sleep, points to a nervous tachycardia. Active carditis can be presumed if in the absence of fever, the sleeping pulse rate approximates the alert rate so as to diminish or abolish the normal variation between the two. A sleeping pulse rate continuously and decisively above the normal is also strong evidence of active heart disease, even though the variation between the rates during sleep and wake persists.

Bradley, W. H. L.: Epidemic Acute Rheumatism in a Public School. Quart. J. Med. **1**: 79, 1932.

Two epidemics of rheumatism are recorded, and their relation to parallel waves of hemolytic streptococcal sore throat is demonstrated, the causal streptococci being of two distinct strains.

Survey of the epidemiological factors concerned leads to the conclusion that droplet infection was responsible for the spread of sore throat and consequently of rheumatism. It is tentatively suggested that rheumatism occurred in those who, being incompletely immunized by a first contact with a rheumatism producing streptococcus, developed hypersensitiveness to that organism.

Campbell, Maurice, and Shackle, J. W.: A Note on Aortic Valvular Disease. Brit. M. J. **1**: 328, 1932.

In a series of cases with disease of the aortic valves, the condition was due to rheumatism in 200, to syphilis in 55, to asthma in 20 and to all other causes in 21 cases. Out of every 6 rheumatic cases roughly, three had aortic incompetence and mitral stenosis, one had both with aortic stenosis as well, one had aortic stenosis and incompetence and one had aortic incompetence alone. Where there was no mitral disease, there were two men for each woman; where there was mitral disease, there were two men for every three women. They came under first observation at all ages, less commonly before ten or after fifty years. There was so little difference between the ages with and without aortic stenosis that its presence must depend on the severity and nature of the attack rather than on the length of time that had elapsed. Pure aortic stenosis was rarely found, and as far as could be judged from the pulse pressure, the stenosis was relatively unimportant compared with the regurgitation even where the signs were well marked.

Among the syphilitic cases, there were three men for each woman, nearly four-fifths being between forty and sixty years. Aortic stenosis was rarely ever

present, and the average pulse pressure was much greater than in the rheumatic cases.

Nearly all the atheromatous cases were men between fifty and eighty years. Aortic stenosis was more important and more frequently present, and signs of regurgitation were often absent.

Auricular fibrillation was present in 30 per cent of those who also had mitral stenosis, in 8 per cent of the rheumatic cases without mitral stenosis, and only rarely in the nonrheumatic group. Left ventricular preponderance was found in about half the electrocardiograms of those with pure aortic disease, normal limits being found in the remainder. The T-waves were inverted, most often in Lead I, in about one-quarter of the rheumatic cases and in about half the others.

The prognosis was enormously better in the rheumatic group. The average duration of life after the development of aortic incompetence was probably twenty years, excluding those who died quickly from active rheumatic carditis. In the syphilitic group, on the other hand, it was not much more than two years after the development of symptoms, few patients living for eight years.

Ellis, Laurence B., and Weiss, Soma: A Study of the Cardiovascular Responses in Man to the Intravenous and Intra-Arterial Injection of Acetylcholine. J. Pharmacol. and Exper. Therap. 44: 235, 1932.

A study was made of the effect of the continuous intravenous injection of acetylcholine in 17 normal human subjects and of the intra-arterial injection in 4 normal subjects. During intravenous injection the following observations were made: The action of the drug was found to be transient, since a given rate of injection could be maintained for a prolonged period of time with no evidence of cumulative action, and since the effects disappeared very rapidly following cessation of the injection. The rate of injection necessary to produce minimal effects was between 0.02 and 0.06 gram per minute, and the maximum tolerated dose was an amount given at a rate of between 0.09 and 0.14 gram per minute. The largest total amount injected was 1.0 gram in ten minutes.

The symptoms produced were flushing of the head and upper part of the body, throbbing in the head, palpitation, sweating, salivation, lachrymation, substernal constriction, nausea and vomiting.

Either no effect or a slight rise in the cardiac rate occurred. In only 3 of 13 cases was there any appreciable lowering of systolic or diastolic arterial blood pressure. In 5 cases in which cardiac minute volume outputs were estimated, no significant change was observed. In each of 5 instances there was a slight increase in the basal metabolic rate.

During the intra-arterial injection of acetylcholine there was marked regional dilatation of the arteries and arterioles, as evidenced by flushing, increase in skin temperature, increased arterial pulsation and increased blood flow. Evidence was found that this increase in blood flow continued for nearly thirty minutes following the cessation of the injection, although the symptoms and flush disappeared much more quickly. That is, although the destruction of the drug in the body was almost instantaneous, the effects of its action persisted for some time. No general systemic effect was noted following the intra-arterial injection of the drug.

It is suggested that the inactivation of acetylcholine probably occurs during its passage through the capillaries. The effects of acetylcholine administered intravenously to man and anesthetized animals are qualitatively similar, but man is very much more tolerant to the drug than are animals.

The theory that acetylcholine acts as a general hormone in the human body and normally circulates in the blood stream is unlikely. Unless acetylcholine acts in

disorders of the arteriolar system differently than in normal subjects, it cannot be considered a useful therapeutic agent in such conditions.

Krogh, A., Turner, A. H., and Landis, E. M.: A Celluloid Capsule for Measuring Venous Pressures. J. Clin. Investigation **11**: 357, 1932.

A celluloid capsule for the determination of venous pressures is described. This capsule is very easily made, and notches can be cut so that it will fit any arrangement of veins. It is cemented to the skin with collodion. When with high venous pressures the necessarily high intracapsular pressure would cause distortion of the skin and erroneous readings, the error can be avoided by the use of a counterweighting clamp also described. Such a counterweight is usually needed for the measurement of venous pressures above 30 cm. water pressure.

Harrison, T. R., Calhoun, J. A., Cullen, G. E., Wilkins, W. E., and Pilcher, C.: Studies in Congestive Heart Failure. XV. Reflex Versus Chemical Factors in the Production of Rapid Breathing. J. Clin. Investigation **11**: 133, 1932.

Studies have been made of the respiratory rate and depth, the minute ventilation, and of the oxygen, carbon dioxide and P_H of the arterial blood and of the venous blood from the brain of dogs anesthetized with barbital. In some experiments artificial reduction of vital capacity was produced either by pneumothorax, by introducing fluid into the lungs through the trachea, or by distending the capillaries of one lung with blood, according to a technic which has been described. In other experiments observations were made concerning the sensitivity of the respiration to oxygen lack, carbon dioxide excess and to acidosis produced by the intravenous injection of ammonium chloride. The following results were obtained.

Reduction of vital capacity by any of the methods used resulted in rapid breathing, provided the vagus nerves were intact. In such experiments chemical changes of the blood were usually either absent or in the direction of increased alkalinity.

In some vagotomized dogs diminution in vital capacity was usually not followed by rapid breathing, unless the diminution was of sufficient degree to produce either marked oxygen lack or increased acidity of the blood.

Oxygen lack produced by rebreathing caused increased ventilation by increase in either depth or rate, or both. In order to double the ventilation it was usually necessary that the arterial blood be less than 60 per cent saturated.

Carbon dioxide excess caused marked increase in depth and relatively slight increase in rate of breathing. The response of the animals to carbon dioxide excess was quantitatively greater and qualitatively different from that of oxygen lack. In order to double the ventilation it was usually necessary to produce a fall of approximately 0.10 in P_H and a rise of 10 mm. Hg in carbon dioxide tension of the arterial blood.

The effect of the acidosis produced by ammonium chloride on the breathing was unlike that of carbon dioxide excess and rather similar to that of oxygen lack, being characterized by a relatively great increase in rate and only slight increase in depth. Following the injection of ammonium chloride apnea sometimes occurred.

Chemical changes in the blood never produced the extreme degree of tachypnea which resulted from diminished vital capacity.

Vagotomized dogs, although insensitive to diminution in vital capacity, reacted with increase in ventilation to chemical changes in the blood.

From these observations the following conclusions have been drawn.

Orthopnea and the continuous dyspnea at rest which occurs in the terminal stages of cardiac disease are of reflex origin and dependent on diminished vital capacity.

It is probable that the rapid breathing found in various diseases of the thoracic organs accompanied by decrease in vital capacity is essentially of reflex origin.

The reflex mechanism of respiratory control is more sensitive than the chemical mechanism. The respiratory center seems to be much less sensitive to alteration in the composition of the blood than has been generally believed.

Krogh, A., Landis, E. M., and Turner, A. H.: The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood. J. Clin. Investigation **11**: 63, 1932.

The movement of fluid through the human capillary wall was studied by means of a pressure plethysmograph, which collapsed the blood vessels and thus permitted the accurate determination of small changes in tissue volume. It was shown that within certain limits the determination of volume change was not significantly influenced by hyperemia or by previous engorgement of the veins. Fluid accumulated in the tissue spaces when venous pressure was greater than 15 or 20 cm. water. Above an average venous pressure of 17 cm. water, the rate of filtration was directly proportional to the increase in venous pressure. A unit rise in venous pressure (1 cm. water) increased the filtration rate by 0.0023 c.c. per minute per 100 c.c. of arm.

The rate at which fluid was removed from the tissue spaces depended on the size of the accumulation of fluid, being distinctly more rapid with large amounts. When less than 0.6 c.c. of fluid per 100 c.c. of arm was present, the removal of fluid was retarded by elevating venous pressure to 15 or 20 cm. water, which was taken to indicate that small amounts of fluid were removed chiefly by true absorption. When more than 0.6 c.c. of fluid per 100 c.c. of arm was present, the fluid was removed in spite of slight grades of venous congestion. In this connection the relative importance of tissue turgor and lymphatic drainage is briefly considered.

When the colloid osmotic pressure of the blood was elevated by standing, the rate of filtration produced by a given venous pressure was uniformly lower. A unit rise of colloid osmotic pressure (1 cm. water) was accompanied by a fall in filtration rate varying between 0.0027 and 0.0045 c.c. per minute per 100 c.c. of arm.

The observations are discussed with reference to capillary pressure and fluid balance in man.

Payne, Sheldon A., and Peters, John P.: The Plasma Proteins in Relation to Blood Hydration. VIII. Serum Proteins in Heart Disease. J. Clin. Investigation **11**: 103, 1932.

In patients with heart failure serum albumin is frequently reduced. Although edema of heart failure may occur even when serum protein and serum albumin are at or above the normal level, it is more commonly associated with some degree of albumin deficiency. The albumin deficits appear to be directly referable to malnutrition.

Gallavardin, L., and Veil, P.: A Case of Permanent Bradycardia with a Rate of Forty. Arch. des Maladies du Coeur, 1928, iv, 210.

The author reports the case of a man of sixty-one years with hypertension following two attacks of hemiplegia and pseudo bulbar signs. The pulse rate at this time was 40 per minute, sometimes lower; except for a rare irregularity, the rate was regular. Amyl nitrate and effort made no difference in the bradycardia.

Auscultation revealed a periodic increase in the vibratory and booming qualities of the heart signs due to the superposition of auricular and ventricular contractions.

The electrocardiogram showed an auricular ventricular sequence but the relation between auricular and ventricular complexes varies constantly. Sometimes before, sometimes superposed and sometimes following the ventricular complex. When the distance between the ventricular and auricular complex was great, the ventricle regained its irritability and a contraction occurred with the appearance of bigeminy. Normal rhythm was restored with subcutaneous injection of .01 gm. of pilocarpine nitrate.

In this case, one could eliminate such diagnosis as partial or total block and sinus bradycardia with ventricular escape.

Two interpretations were considered: first, nodal rhythm with an upright P-wave. The slow rate, the constancy of the association between auricular and ventricular make it resemble permanent nodal rhythm. In the tracing, P-wave first preceded QRS, then was superposed, then followed it, and the only difference between this and nodal rhythm was that the P-waves were uniformly upright. Because of this factor the authors do not think it is a case of nodal rhythm. Second, a possible interpretation is an arrhythmia of the entire A-V cycle. Admitting it only as a hypothesis, the authors based their belief on the constancy of this association of the auricles and the ventricles.

They consider whether some higher center might be responsible for this altered rhythm and attempt to correlate it with the pseudobulbar palsy of the subject.

Geraudel, E.: Paroxysmal Tachycardia. Arch. de Malad. du Coeur, 1928, v, 273.

The author cites two cases of paroxysmal tachycardia of long duration. Both cases could have been mistaken for the auricular ventricular form of the condition were it not for the electrocardiograms taken during freedom or comparative freedom from attacks. In both instances, the tracings made during the crises showed a position of the P-wave closer to the preceding R-wave than to that following. This gives the impression of nodal rhythm.

During the intervals between attacks, flutter with a varying auricular to ventricular ratio was present. 2:1 in the case of 1 subject and 2:1 to 3:1 in the case of the other. During a period where attacks were followed by periods of freedom, the auricular rhythm was constant while that of the ventricle became grouped in series of 2 and 3 and 4 ventricular beats. This quadrageminy was shown to merge easily into that of paroxysmal tachycardia; as it did so the P took a position closer to the preceding R than to the one following.

The author concludes that paroxysmal tachycardia of auricular ventricular or sinus origin does not occur, both being phases of auricular tachycardia or flutter where there is an iso-arrhythmia of auricle and ventricle. No new centers dominate the rhythm, but rather a variation was present in the harmony of the response of the auricles and ventricles.

Geraudel, E.: Auricular Tachysystole and Auricular Fibrillation, 1928, v, 289.

In a second paper, the author attempts to show that the difference between auricular flutter and fibrillation is only one of degree. The definition of flutter as a condition with a rapid rate and a definite ratio between the auricular ventricular rate is not sufficiently exact. The author's definition is that of a rate more or less rapid and showing under prolonged observation a lack of co-ordination between the auricular and the lowered ventricular rates.

The term total arrhythmia for fibrillation is to be discouraged as it differs in the pulse and such an arrhythmia of the pulse may be produced by other conditions than fibrillation. The complexes resemble those of flutter and for these the term flutter fibrillation was used. This has been supposed to be a combination of the two arrhythmias, the periods of fibrillation depending on the change in the refract period of the muscle.

The author considers this to be wrong and based on the wrong assumption that changes in the form of the P-wave are due to changes in the excitation wave in the auricle. The P-waves of flutter may resemble those of fibrillation by other influences and so be recorded by the string. The abnormal shape of the P-wave in the fibrillation periods may be due to a rapid rate, for although fibrillation waves may be present with an apparent rate of 75, they are commoner with the auricle beating between 400 and 600 per minute. Two facts are evident in the study of fibrillation—the rapid rate and the inconstancy of the rhythm.

The author therefore considers the difference between auricular flutter and fibrillation is that in the former the rate is 130 to 400 and constant, while in the latter it is 475-600 and variable. He suggests that the term tachyatrie monorhythmique for flutter and for fibrillation the term hypertachyatrie poikilorhythmique.

Book Reviews

DER HERZALTERNANS. By Bruno Kisch. Dresden and Leipzig, 1932, 214 pp., Theodor Steinkopff.

Dr. Kisch, Professor of Physiology at the University of Cologne, presents a most comprehensive study of the difficult and complicated subject of alternation of the heart. He not only has studied the literature thoroughly, but has carried on experimental work for twelve years.

The author devotes the first third of the volume to a brief discussion of what the term means and to a detailed consideration of the various methods—physical, graphic and electric—by which alternation has been studied. He then describes and illustrates seven different disturbances which may produce alternation, namely, alternating partial asystole or hyposystole, alternating partial hypodiastole or adiastole, alternating asystole and adiastole of different parts of the heart muscle, alternation of total systole, alternation of impulse formation or conduction, and alternation of the filling and emptying of the heart produced by hemodynamic factors. He believes that in the last analysis an understanding of this complex subject will depend upon an understanding of chemical and physicochemical changes in the heart muscle. In the section devoted to factors which affect alternation the author discusses inherent properties of heart muscle, the influence of various salts and poisons, rate, extrasystoles, conduction, the coronary circulation, temperature, and the cardiac nerves. Finally he discusses, relatively briefly, the relationship between alternation and other disturbances of the circulation and the clinical features. He provides twelve pages of references and a carefully prepared index.

This study, which must represent a tremendous amount of work, is of scientific rather than clinical interest. The bibliography alone would be valuable to anyone interested in the subject, and the subject will remain open until the chemical and physicochemical properties of heart muscle which Dr. Kisch stresses are much more fully understood.

E. H.

DER WASSERVERSUCH ALS NIERENFUNKTIONSPRÜFUNG. Von Dr. Med. Ferdinand Lebermann, Fachartz für Innere Krankheiten in Würzburg. Dresden und Leipzig, 1932, pp. 145, Theodor Steinkopff.

In this study not only is the attempt made to determine the advantages and limitations of the dilution and concentration tests (as they are generally called in this country), but also these tests are used as a means of approaching the intricate problem of water balance and metabolism in the body. The questions at issue touch various phases of Bright's disease especially, but are not restricted to this disease; the discussion extends to diabetes insipidus.

In considering the various theories of water excretion through the kidney the author seems to find himself cramped, since it is not always easy to harmonize experience in the clinic with any theory so far propounded. There is throughout the essay a constant reference to extrarenal factors which in some relations only are known at present. Specifically is cited the observation of Marx, that the ingestion of relatively small amounts of water induces as much "dilution" of the blood when measured by hemoglobin changes as does the ingestion of large amounts, and further, that there seemed only a remote relation between degrees of blood dilu-

tion and maximal urine excretion. Lebermann studies this question of water content of the blood along with the volume of urine excreted hour by hour during the dilution and concentration tests.

In American clinics the selection of even quite accurate hemoglobin estimations as a means of determining the water content of blood (or more probably blood volume), would be regarded as unfortunate.

Lebermann uses the dilution test in the conventional manner of Volhard and Strauss, except that one liter, rather than a liter and a half, of water (or tea) is given to the fasting patient, and the urine is collected hourly for four hours. The concentration test is carried out during the afternoon of the same day; a sequence which has been much criticized and largely abandoned in this country. From these two tests information may be gained bearing on the functions of excretion, dilution and concentration. In Lebermann's opinion impairment of concentration is the chief diagnostic point.

About one-half the monograph is devoted to the study of various types of Bright's disease by means of these tests. The theoretical assumption that according to the location of the lesion in the kidney the water test should demonstrate typical disturbances in the renal capacity for excretion, dilution or concentration does not work out perfectly; differential diagnosis is accurate only within certain limits. For example, a case of nephrosis with variable edema gave responses resembling acute glomerulonephritis with dropsy. In acute glomerulonephritis of the post-anginal type the dilution and concentration tests were practically normal, indicating, it was assumed, extrarenal factors. Likewise, with cases of early chronic glomerulonephritis and also with nephrosclerosis, the tests may fail to give results which are essentially informing.

The attempt to use these tests as a means of recognizing various types of Bright's disease is based on dubious reasoning. In so far as they are of value, they measure the degrees of defect, and to assume that a degree of defect is peculiar to a type of renal disease, and is specific, is not in harmony with what is known today. Moreover, the tendency of recent years is to regard nephritis less and less as a disease of the kidneys, but rather as a constitutional disorder in which the kidneys are implicated; hence the return of recent writers to the term Bright's disease.

In order to estimate extrarenal factors, particularly cardiac, and also to find a method of using the dilution and concentration tests in prognosis, Lebermann had recourse to the use of diuretic drugs along with the Volhard test. The drugs used range from digitalis through diuretin and urea to salyrgan. The author derived an encouragement from his experience which the reviewer cannot share.

There is an extensive bibliography which omits several relevant English and American names.

N. B. F.

LE NEUROSI DEL CUORE E DEI VASI SANGUIGNI E LORO CURA. By Professor Giovanni Galli (University of Pavia) Milan, Societa Editrice Libraria, 1930, pp. 361.

(The Neuroses of the Heart and Blood Vessels and Their Treatment) In this lucidly written book Professor Galli presents his ideas and observations concerning the functional disturbances of the circulatory system. He speaks of their increase in modern times with the comment that a true civilization is one which should prevent illnesses rather than cause them.

He gives an historical account of various treatments of the neuroses throughout the ages, beginning with those employed in the temples of Aesculapius, continuing on through mesmerism, osteopathy, Christian Science, Couéism, and finally psycho-analysis.

He considers the influences of diets, poisons, drugs and hormones on the heart and blood vessels. He classifies and describes the various tachycardias, and considers in turn extrasystoles, palpitations, mitral neurosis, respiratory arrhythmias, hypotension and hypertension on a neurotic basis, and then discusses visceral, skin and arterial vasomotor disturbances, and finally the circulatory neuroses on a sexual basis.

He treats occurrences, causes and medications in a well-ordered, interesting manner, guided by a sound insight and well-balanced evaluations.

While considering psychoanalysis of the greatest value in treating the neuroses, he pays due regard to the use of medical and surgical therapies.

The author's definition of a neurosis is of special interest. He says: "A neurosis is a disease of the small blood vessels accompanied by both physical and chemical lesions which are, as a rule, completely curable. The signs and symptoms, diverse in character, vary according to the organ or part in which the attendant circulatory disturbance occurs. Psychic influences play an important rôle." He considers such an interpretation a working point for research, and one which further investigations will substantiate, rather than one already proved. He admits the lack of instruments and objective proofs to support this viewpoint in most cases, but calls attention to the fact that in accessible organs these proofs are not wanting, as may be seen in the vessels of the eye, larynx and extremities.

He quotes Sawitzky, (*Ztschr. f. Kreislaufforsch.* 1929, 1) who in his experiments in cases of mitral neurosis has shown evidences of spasm in the papillary muscles of the heart as the cause of incomplete occlusion of the mitral valves.

In addition the book contains excellent anatomical and physiological considerations, interesting case reports, and a description of the technic of psychoanalysis.

A. R. B.